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THE RATES OF GROWTH, OSSEOUS DEVELOPMENT, AND MENTAL DEVELOPMENT IN CRETINS AS A GUIDE TO THYROID TREATMENT

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WE ARE presenting a simple method of following and comparing the rates of growth, osseous development, and mental development in cretins, and shall show how it is of special help in following the results of therapy and in regulating the dose of thyroid extract.

It has been known for many years that the cretin is stunted in height and retarded in development. As long ago as 1896 Hertoghe[1] demonstrated by x-ray the delay in the ossification of the carpal bones. Since then numerous workers have shown that there is always a delay of the time of appearance of the various centers of ossification in cretinism and in juvenile hypothyroidism. Englebach and McMahon,[2] Shelton,[3] Canelo and Lisser,[4] Shephardson,[5] Dorff,[6] and others have demonstrated that the administration of thyroid extract causes a rapid acceleration of the osseous development. Shelton[3] has considered that the rate of osseous development is "an index of metabolic speed." However, it is important to emphasize, as Shephardson[5] and others have done, that retardation of osseous development is found also in certain types of dwarfism which are not due to hypothyroidism.

Gesell, Amatruda, and Culotta[7] have recently published observations on the effect of thyroid therapy upon the mental and physical growth of cretinous infants. They have made elaborate studies of the mental development and behavior patterns, the height index and other anthropometric measurements, but they have not recorded especially the rate of development of the osseous system.

METHODS

In order to permit a comparison between growth in height, osseous development, and mental development, we have reduced the measurements to terms of "height age," "bone age," and "mental age" in the following manner:

From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics, Johns Hopkins Medical School.

Height Age.—The standing height is measured in the usual manner. A comparison with the standard anthropometric tables* shows the age at which the "average" child of the same sex will attain this height, and this is considered the patient's "height age." For example, our patient is a boy of four years who is 34.4 inches tall. The tables show that the average height for a boy of two years is 34.0 inches and for a boy of two and a half years is 34.8 inches. Our patient's "height age" is then recorded as two and a quarter years.

Bone age is determined by a study of the various centers of ossification shown by roentgenograms of the joints and a comparison with Shelton's tables[9]† showing the normal time of their appearance. In instances where

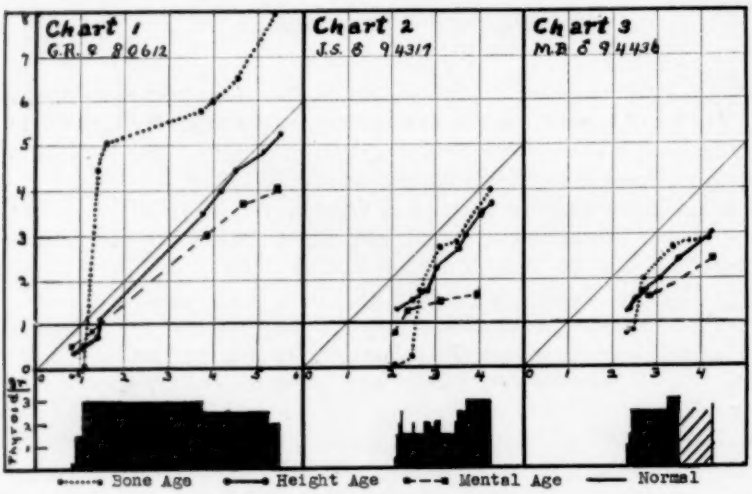

Fig. 1.—Cretins treated with thyroid.

there is a discrepancy in the level of osseous development at different joints, the average level of development is taken as the bone age.

Mental age is determined in infancy by the development schedules devised by Gesell, and later by the Stanford revision of the Binet-Simon tests.‡

*We have used the anthropometric norms compiled by Englebach,[8] taking as average for a particular age the mean between the minimum and maximum measurements of this age.

†The more recent roentgenographic studies of the normal osseous development have been made by Allen,[10] Paterson,[11] Sawtell,[12] Shelton,[9] Todd,[13] Pryor,[14] Stettner.[15] There is considerable difference of opinion in regard to the normal time of appearance of the various osseous centers. Hodges[16] has shown the normal variations in the time of appearance in the epiphyseal chart which he has devised. The tables of Shelton[9] probably have the advantage of showing the "average" time of appearance. In constructing graphs we are compelled to use averages for osseous development just as we use the average for height. As shown by Pryor[14] and Sawtell,[12] there is probably a sex difference in the development of the osseous system, the female developing more rapidly than the male. This should probably be taken into consideration, although the difference in the first few years of life is only a matter of months.

‡Examinations made by Dr. Leo Kanner and members of the psychiatric group at the Harriet Lane Home.

Graphs of Developmental Rates.—The height age, bone age, and mental age are each plotted as graphs on the same chart in accordance with observations made from time to time while the patients are receiving thyroid medication. In the charts the patient's chronologic age is plotted along the abscissas and the developmental age along the ordinates. The normal rate of development is represented by a straight line rising at 45 degrees from the horizontal. The relative position of the graph of height age, bone age, or mental age in respect to the normal line indicates the deviation from normal of each of these developmental processes. Likewise the position of the graphs in relation to each other indicates which of the developmental processes is the more retarded.

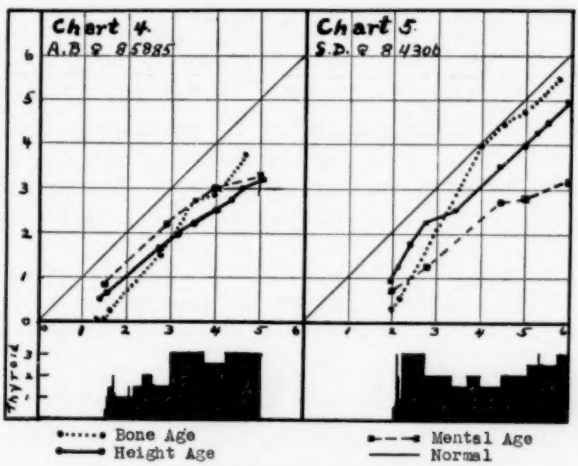

Fig. 2.—Cretins treated with thyroid.

The daily dose of thyroid* administered is shown at the foot of each chart. A solid black area indicates that the prescribed dose was given regularly, and a shaded area that the medication was irregular or interrupted.

We realize that absolute norms cannot be established for any of the developmental processes and that minor deviations in a particular case must not be taken too seriously. However, the general developmental trend in relation to the normal rate is of significance and shows whether the patient's development is paralleling the normal rate, exceeding, or lagging behind it.

DEVELOPMENT LEVELS OF CRETINS BEFORE TREATMENT

Figs. 1, 2, and 3 show the developmental charts of six cretins who came under observation between the ages of eleven and twenty-seven months. They all showed characteristic features of cretinism: marked delay in

*Armour and Company's desiccated thyroid was used exclusively in this study.

mental development and activities, dull phlegmatic disposition, cretinoid facies, large abdomen, dry scaly skin, coarse scanty hair, and secondary anemia. The basal metabolic rates could not be determined.

The developmental levels and the fasting levels of blood cholesterol before treatment are given in Table I.

TABLE I

CASE	H. L. H. NUMBER	SEX	CHRONOLOGIC AGE (MONTHS)	BONE AGE (MONTHS)	HEIGHT AGE (MONTHS)	MENTAL AGE (MONTHS)	BLOOD CHOLESTEROL (MG. PER 100 C.C.)
1	80612	F	11	0*	4	3	145
2	94317	M	25	0	16	9	258
3	94436	M	28	9	15	?	203-250
4	85885	F	16	0	6	9	201-298
5	84306	F	24	3	12	8	209
6	81573	F	19	0	9	?	221

*0—indicates that the development was that of the newborn infant.

There was marked retardation in bone age, which in four instances was at the newborn level, in one instance three months, and another nine months. Parallel with the osseous retardation there was marked delay in the dentition, none of the children having any teeth. The height age was retarded *but to a much less degree than the bone age.* The determination of the mental age before treatment was attended with great difficulty because of the characteristic mental torpor of the untreated cretin. In general it may be said to be retarded to approximately the same degree as the height age.

DEVELOPMENTAL RESPONSE TO TREATMENT

These patients were all treated with desiccated thyroid in doses varying from 1 to 3 grains (0.064-0.192 gm.) daily. With the beginning of therapy there was a rapid loss of torpor and an increase of the infant's general activity which superficially gave the impression of rapid mental development. The skin and hair rapidly became normal, and the fat pads were lost. In a short time the cretinoid facies and habitus had almost completely disappeared.

In the developmental curves which we have plotted, the acceleration of the osseous development is most striking. Following a delay of two to four months, there was a rapid appearance of new centers of ossification so that the bone age rose rapidly, approaching the normal developmental level and sometimes exceeding it, as in Case 1. Before therapy the bone age was uniformly below the height age. Under adequate thyroid medication the bone age rose more rapidly than the height age, passing above it. In five cases the height curve approximately paralleled the normal, but at a lower level, so that there continued to be a relative stunting for the age. However, in Case 1 the height reached the normal for the age. Following the initial increase in the infants' activities and responses to environment, the rate of mental development was less spectacular. In

Cases 1 and 4 the rate of mental development* was almost parallel with the height age, but at a lower level. In the other instances there was a decided lag below the normal.

DEVELOPMENTAL RATES AS A GUIDE TO TREATMENT

That the developmental curves, particularly the rate of osseous development, serve as an indication of the adequacy of thyroid therapy is illustrated by the two following cases:

CASE 6.—M. C., No. 81573, female (Chart 6). The child was first seen in March, 1933, at the age of one year and seven months. She presented all the clinical features of cretinism with typical cretinoid facies, coarse rough skin, and scanty dry

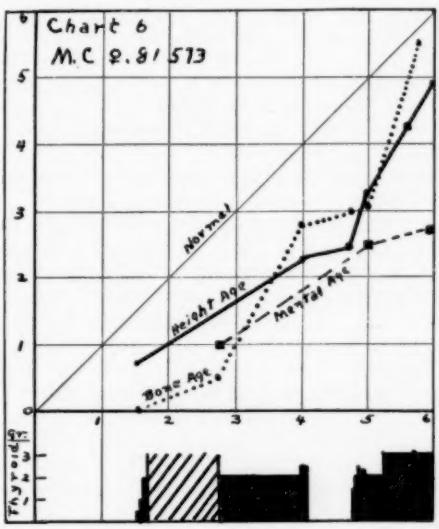

Fig. 3.—Cretin treated with thyroid.

hair. Her height was 27.6 inches, the average height of a nine-month-old female. The osseous development was that of the average newborn. There were no teeth. The mental development was less than that of a six-month-old baby. Treatment was begun with a dose of ½ grain (0.032 gm.) thyroid daily. The dose was increased by steps to 3 grains (0.192 gm.) daily at the end of three weeks. It was subsequently learned that from the age of twenty to thirty-two months the thyroid was given in smaller doses or omitted entirely by the mother because of the occurrence of toxic symptoms such as irritability and diarrhea. This period of irregular treatment is represented on Chart 6 by the shaded area. Both the "height age" and the "bone age," although increasing slowly, lagged behind the normal rate of development. In May, 1934, at the age of thirty-three months, the child's bone age had reached the level of six months. The height, at this time, was not recorded in the history, but from a reconstruction of the curve it probably did not exceed an

*It should be noted that we have recorded mental development in terms of "mental age" rather than "intelligence quotient." When the difference between the chronologic and mental age remains the same, the intelligence quotient actually rises as the patient grows older.

eighteen-month level. The level of mental development was estimated to be approximately that of a twelve-month-old child. In spite of the subnormal rate of physical and mental development the child had become more active and energetic and had lost her cretinoid stigmas. Her skin had become soft, moist, and warm, and her hair had grown and become normal in texture. At the end of this period the blood cholesterol was 121 mg. per 100 c.c. These facts led the attending dispensary physician to believe that the patient was being adequately treated and that a satisfactory result was being obtained. In fact the occasional occurrence of toxic symptoms when 3 grains (0.192 gm.) were administered suggested that she had been overtreated. However, the study of the developmental curves showed that the thyroid actually received over this entire period had been insufficient to maintain a normal rate of development, much less to accelerate it so as to approach the normal level.

In April, 1934, the dose of thyroid was reduced to 2 grains (0.128 gm.) daily. With this reduction toxic symptoms no longer occurred, and better parental cooperation was obtained. From the age of thirty-two to forty-nine months the thyroid was given regularly. Then, for the first time, there was rapid acceleration of the developmental rates—manifested principally by the rapid bone development which increased from an age level of six months to two and three-quarters years. The bone age increased more rapidly than the height age, which reached only two and a quarter years. The progress in mental development was about parallel with the height.

In September, 1935, when the patient was forty-nine months old, the parents again became uncooperative. They failed to give the child any thyroid until April, 1936, when she was fifty-six months old. During this period of seven months there was a marked retrogression in her condition. She became dull, stupid, and phlegmatic; her features became heavy and cretinoid, the skin and hair dry and coarse and the color pale. She gained 7 pounds in weight. As shown by the graph, there was very little increase in either the height age or bone age.

In April, 1936, at the age of fifty-six months, thyroid treatment was resumed, with a dose of 2 grains (0.128 gm.) daily which was increased to 3 grains (0.192 gm.) daily in November, 1936. Clinical improvement was prompt. There was an immediate acceleration of the rate of growth (height age) and after a lapse of three or four months, a still greater acceleration of the bone development. In August, 1937, at the age of six years, the child's bone age had increased to five and a half years and her height age to five years. The mental development progressed more slowly and was only two and three-quarters years.

CASE 7.—J. C., No. 49616, male (Chart 7) was born in May, 1924. This boy was first brought to the Harriet Lane Home in 1927 at the age of three years, but unfortunately his record between that time and January, 1930, is lost. He had learned to walk alone shortly before his second birthday. A swelling in the thyroid region was noted at three years. He returned to the Harriet Lane Home in May, 1930, at the age of six years, having had no treatment. He was described as small and having a "myxedematous expression."[5] The skin and hair were dry and coarse. The thyroid gland was two or three times the normal size, soft and not nodular. The child appeared dull and phlegmatic and could not talk. He suffered from chronic constipation. At this time the chronologic age was six years, "height age" four years, and "bone age" two and a half years. The mental age was thought to be about two and a half years. Thyroid, ½ grain (0.032 gm.) daily, was prescribed and was given regularly. Marked improvement in his activity and in his mental development followed, so that at the age of six years and eight months, a restandardization showed a mental age of four years, four months. Repeated measurements of the basal metabolic rate were made and reported as +7, +12, +20, +12, ±0, +22, −6, +11, +17, +9 (Boothby-Sandiford standards). On one occasion in 1931 after withdrawal of thyroid medication for three weeks a drop of the basal metabolic rate

from +22 to −4 occurred, and on another occasion in 1934 it dropped from +17 to +9 when thyroid was withheld for four weeks, and to −11 at the end of three months. On this last occasion the blood cholesterol rose from 114 mg. per cent to 208 mg. per cent after four weeks of privation and to 405 mg. per cent after three months. Owing to the facts that the basal metabolic rate was constantly well on the plus side and that the child no longer showed any clinical features of hypothyroidism, the various attending physicians in the dispensary considered that the patient was receiving an adequate dose of thyroid. The dose was maintained at ½ grain (0.032 gm.) daily for over three years until September, 1933, when the patient was nine years and four months old. Then the dose of thyroid was raised to 1 grain (0.064 gm.) daily, and in November, 1934, at the age of ten years and six months, it was further increased to 1½ grains (0.096 gm.) daily. During this period of five and

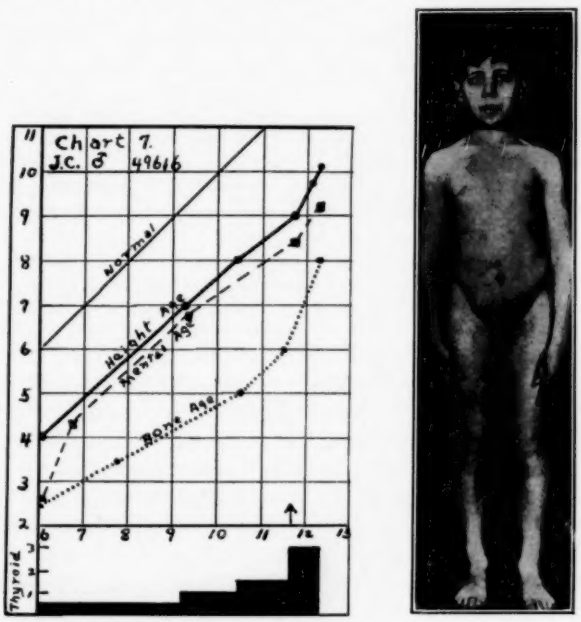

Fig. 4.—Cretin inadequately treated.
February 5, 1936. Chronologic age, eleven years, nine months; height age, nine years; bone age, six years; mental age, eight years, six months; weight, +11 per cent.

one-half years of constant observation, roentgenograms of the bones had been taken on several occasions, and the height had been recorded once or twice. Unfortunately, no attention had been paid to these observations in following the patient's progress.

The boy was admitted to the Endocrine Clinic in February, 1936, at the age of eleven years and nine months. At this time he was rather dull and phlegmatic. There was nothing about his general appearance, skin, hair, or body build to suggest cretinism or juvenile hypothyroidism. The height age was nine years. Roentgenograms taken three months previously showed a bone development of six years. The mental age was eight years, eight months. The blood cholesterol was 178 mg. per cent. On reviewing his case, we plotted his developmental rates from the age of six years. As shown by Chart 7, it was obvious that thyroid had caused no acceleration

in the rate of the patient's bone development until the dose had been increased to 1½ grains (0.096 gm.) daily; on the contrary, the bone age had fallen further and further below the normal level. The growth in height had also fallen below but to a less degree. At the onset of treatment there had been a preliminary acceleration of the boy's mental processes, but after this the mental development had lagged below the normal rate. We felt that the continued retardation in all the developmental processes indicated that the boy had not received sufficient thyroid and that the basal metabolic rate figures should be disregarded. It seemed reasonable that, if we wished to accelerate development sufficiently to approach the normal level, it might be necessary to produce some degree of hyperthyroidism.

The dose of thyroid was increased by increments of ½ grain (0.032 gm.) every third day until the patient was receiving 3 grains (0.192 gm.) daily. The pulse rate rose from 80 to 112 for the first four months, then dropped to 96-100. The blood pressure rose to 130/68-120/76 and remained at this level. There were no unpleasant or toxic symptoms such as excessive sweating, palpitation, or nervousness, and the boy's general condition seemed improved. The cholesterol dropped from 178 to 136 mg. per cent. The basal metabolic rate determinations were recorded as "fairly satisfactory" and on several occasions were +16. In the twenty months since the dose of thyroid was increased to 3 grains (0.192 gm.), there has been for the first time a definite acceleration in the rate of bone development, growth in height, and mental development, as shown by Chart 7. Whether this accelerated rate will be maintained, or whether a further increase in the dose will be required remains to be seen.

We believe that this case illustrates the importance of following the developmental rates and the fallacy of placing too much reliance on the basal metabolic rate as ordinarily determined, in the regulation of thyroid medication.

REGULATION OF THE DOSE OF THYROID IN THE TREATMENT OF CRETINS

In treating a hypothyroid infant or child, the objective should be to bring the patient as close as possible to the normal level of physical and mental development. When there is a deficiency of thyroid, the lowered level of metabolism apparently leads to a retardation of all the developmental and growth processes. It seems probable that if just sufficient thyroid is supplied to fulfill the usual body needs, the developmental processes proceed at the normal rate, parallel to but not approaching the normal level. In order to accelerate the developmental rate sufficiently to allow the retarded hypothyroid patient to regain his lost years and approach his normal age level, it is probably necessary to produce a mild degree of hyperthyroidism. The rate of development, especially the osseous development, probably gives the most reliable information concerning the average level of cellular metabolism over long periods of time. One cannot be guided by the marked improvement in the cretin's appearance because, even with small doses of thyroid, the child rapidly becomes more active and energetic, the excess weight is lost, the skin becomes soft, warm, and moist, and the cretinoid facies disappears. The improvement may be deceptive, and the child's development may continue to lag below the normal rate. This can be determined only by following the developmental rates as we have done. If the osseous development after a few months does not approach the normal level, the dose of thyroid is probably inadequate.

In determining the patient's immediate tolerance to thyroid, one of course cannot be guided by the developmental rates. One should aim to give as much thyroid as the individual can tolerate without the production of unpleasant toxic symptoms. These symptoms are usually cramps, diarrhea, vomiting, excessive irritability or twitchings, or a very rapid pulse rate. Such disturbances should lead to an immediate reduction of the dose. On the other hand, mild symptoms of hyperthyroidism may be disregarded. The cretins who have previously been phlegmatic and amenable may become very hyperactive, irritable, distractible, and hard to manage as are other mentally deficient children. There may be considerable loss of weight and sweating. It is our rule to start the cretin, even if less than one year of age, with ½ grain (0.032 gm.) of thyroid extract daily. This dose is increased by increments of ½ grain at intervals of a week until slight toxic symptoms occur. The patient should be under close observation during this period, and hospitalization is preferable. Most cretins will tolerate 2 to 3 grains (0.128 to 0.192 gm.) of thyroid daily, although occasionally a smaller dose is necessary. This is usually given in two or three divided doses. If toxic symptoms occur—and the mothers will usually complain very definitely of these—the thyroid should be omitted for a few days and then resumed at a level ½ grain below that previously given. Not infrequently an infant may be somewhat sensitive to thyroid when treatment is first started but may later acquire increased tolerance and require a larger dose. We have not seen any cretins, either in infancy or later childhood, who required more than 3 grains (0.192 gm.) of thyroid daily in order to show a marked acceleration in the rate of osseous development. Kerley,[17] in reporting a number of cretins whom he had followed for twenty years or more, states that in later childhood many of these patients acquired increased tolerance and required as much as 10 to 12 grains (0.640 to 0.768 gm.) of thyroid daily, although after reaching puberty their tolerance again decreased. We have not encountered such cases, and we wonder whether his experience was due to the fact that thyroid extract was not standardized before 1929.

After the tolerance for thyroid has been determined, the patient still should be kept under frequent observation, and the mother must be impressed with the necessity of maintaining continuous therapy for the rest of his life. X-rays should be taken to study the centers of ossification, first at intervals of three or four months, later every six months or year. The height should be recorded regularly and mental standardizations made from time to time. Unless there is a continuous rapid development of the osseous system, one should attempt to increase the dose of thyroid to a higher level.

THE END RESULTS OF TREATMENT

We are not prepared at this time to discuss the end results observed in the treatment of cretins. Kerley,[17] Gesell,[7] Goodkind[18] and others have

shown that some cretins attain normal physical development but remain permanently retarded in mental development. Although this is often attributable to delay in the beginning of treatment, to inadequate dosage,* or to interruptions in the continuity of treatment, it is possible that in some instances an irreparable damage to the nervous system has occurred in the intrauterine period or in early infancy.

SUMMARY

We have reported a method of following and comparing the rates of growth, osseous development, and mental development of cretins under thyroid treatment. The administration of adequate doses of thyroid always causes a marked acceleration in the developmental rates. The bone development always progresses rapidly toward the normal level. The growth increases less rapidly but usually parallels or exceeds the normal rate, whereas the mental development in some instances continues to lag behind the normal rate. The developmental rates, especially the rate of osseous development, serve as a reliable guide to the adequacy of thyroid treatment over long periods, whereas the clinical condition of the patient and the measurements of the basal metabolic rate or blood cholesterol may give a deceptive picture of the amount of improvement. It is probably necessary to produce a mild degree of hyperthyroidism in order to accelerate the developmental rates sufficiently to allow the retarded hypothyroid patient to regain his lost years and approach his normal age level. One should not hesitate to give sufficient thyroid, provided that unpleasant toxic symptoms do not occur.

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*The majority of the cretins who come under our observation after being treated elsewhere have received very small doses of thyroid. A common mistake of the physician is to prescribe an English brand of thyroid (Burroughs-Wellcome) without taking into consideration that this is not standardized according to the *United States Pharmacopoeia*. Lerman and Salter[19] have shown that 1½ grains (0.1 gm.) of U.S.P. (Armour, Lederle or Lilly), 1 grain (0.064 gm.) of Parke, Davis & Company and 5 grains (0.3 gm.) of Burroughs-Wellcome thyroid are each equivalent in calorigenic effect to 0.3 mg. of pure thyroxine.

TREATMENT OF SCARLET FEVER WITH SPECIFIC ANTITOXINS OF LOW PROTEIN CONTENT

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ONE of us previously reported his conclusions on the use of scarlet fever antitoxin.[1] These views were again summarized in a subsequent publication.[2] It was stated that, since scarlet fever had been so mild in recent years, it would be extremely difficult to evaluate the efficacy of scarlet fever antitoxins. It was also claimed that scarlet fever antitoxins often caused reactions more severe than the disease itself.[3]

In a series of 283 treated patients, 38.5 per cent had reactions.[1] The types of reactions referred to have been previously described.[4] Although biological laboratories had had years of experience in manufacturing, concentrating, and purifying diphtheria antitoxins, the experience thus gained did not seem to apply to the production of scarlet fever antitoxins. The reaction rates following the use of scarlet fever antitoxins made and concentrated after such methods were always higher than those which followed the use of diphtheria antitoxin. It was always higher than that rate which followed the use of erysipelas antitoxin. There seemed to be something inherently different in the make-up of scarlet fever antitoxin.

Recently purified and concentrated scarlet fever antitoxins have been manufactured by three different biological laboratories. Two of these have been marketed, while one has been experimentally tested. All of these antitoxins have been used by us. We have treated 800 cases with one antitoxin, termed antitoxin I, 92 cases with antitoxin II, and 30 cases with antitoxin III. The various antitoxins were not available at the same time. Hence the number of cases treated with each kind of antitoxin is not comparable. Our primary objective was to ascertain if the serum reaction rate with these kinds of antitoxins was less than those rates had with other types of antitoxins. This paper is a report of our findings.

ANTITOXIN I

The results obtained in treating 524 of the 800 patients with antitoxin I were tabulated in detail, the experiences with the remaining 176 cases were comparable. This antitoxin contained about 3 c.c. of material in each ampoule. Twenty and six-tenths per cent of the cases were under 5 years of age; 42 per cent between 5 and 10 years, 25 per cent between 10 and 20 years; and 12.18 per cent between 20 and 60 years. Seventy-nine and eight-tenths per cent were white; 20.2 per cent, negroes; 49.3 per cent males, and 50.7 per cent females.

Of the 524 patients who received serum, 59 patients, or a little over 11 per cent, had serum reactions. (One patient had two attacks of

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urticaria which were counted as two reactions.) Of 330 children under 10 years of age, 29 patients, or 8.8 per cent, had reactions. Of the 194 patients over 10 years of age, 30, or 15.3 per cent, had reactions. Only 3 patients, or 0.57 per cent, had immediate reactions; 4, or 0.76 per cent, had accelerated reactions; and 52, or 9.92 per cent, had the usual delayed or late reactions. Table I shows this distribution.

Analysis by age groups will show that the greatest incidence of serum reactions occurred in individuals from 5 to 20 years of age (Chart 1).

TABLE I

SERUM NO.	CASES	NO REACTIONS	IMMEDIATE REACTIONS	DAY OF REACTION AFTER SERUM												
				1	2	3	4	5	6	7	8	9	10	11	12	LATE‡
47H263J	66	63							2	1						
*47H238N	11	9								1						1
47H238M	121	107	1				1		3	1	4	1				3
47H263K	94	79					1	4	3	2		2	1		1	1
47H236N	50	46								1	1	1				1(?)
*47H238K	18	18														
47H236M	35	34								1						
†47H263N	35	30	1	1†		1		1	1	1†						
47H236K	4	3							1							
47H236L	11	9			1								1			
47H238L	3	3														
47H236H	48	41	1				1	1		2		1	1			
47H213R	2	2														
47H203R	1	1														
47H263N	1	1														
47H ?	25	21		1			1		1		1					
TOTALS	*525	467	3	2	1	1	4	6	11	10	6	5	3	0	1	6
				accelerated 4			delayed 52									
% on basis of 524 patients.		89.12%	0.57%	0.76%			9.92%									

*One patient received a double dosage of serum in which one from each of these lot numbers was administered: 525 injections of serum in 524 cases.

†This patient had two attacks of urticaria, one on the day following the administration of serum and the other on the seventh day after serum. Fifty-nine attacks of serum sickness in 58 cases.

‡Day not given.

One patient, allergic to food, had no reaction. One patient who had had a late reaction to tetanus antitoxin some years previously did not have any following the subsequent administration of scarlet fever antitoxin. One patient who had a late reaction also had had a dose of antistreptococcus serum before admission; one patient in the immediate reaction group was given 40,000 units of diphtheria antitoxin in addition to the scarlet fever antitoxin.

We tried to account for every vial of antitoxin by its serial number, but failed to do so in 25 instances. Nevertheless, it can be seen from Table I that the serums of some horses tended to give more reactions than others. Conclusions on this point were not definite since comparable numbers of patients were not treated with the same lot of antitoxin. In

two groups of 35 patients each, treated with lot number 47H236M and lot number 47H263N, respectively, only one reaction occurred with the former antitoxin and five with the latter, one of which was immediate, two accelerated, and two delayed.

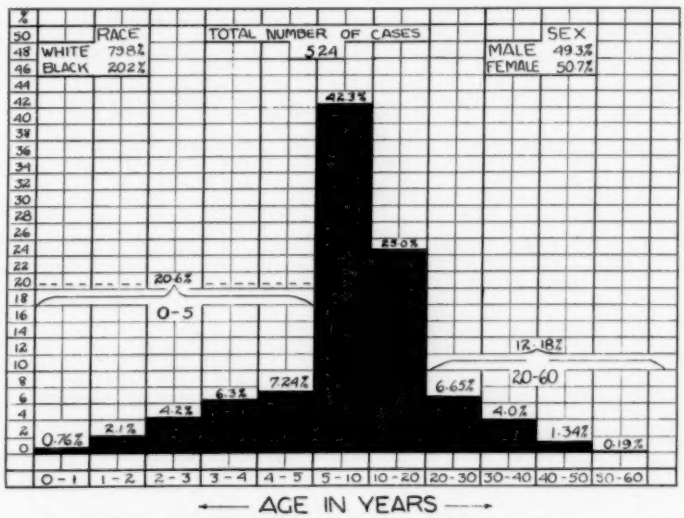

Chart 1.—Percentage distribution of 524 cases of scarlatina with respect to age—ages ranged from 7 months to 52 years.

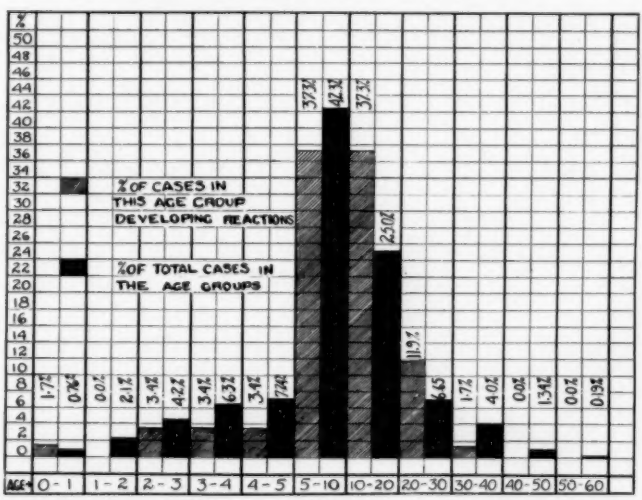

Chart 2.—Comparison of cases developing severe reactions with total cases in each age group.

A greater percentage of the patients who were not benefited by the antitoxin had serum reactions, i.e., 6 per cent of the group that was not ill, 10.7 per cent of the group that was slightly benefited, 9.3 per cent of

the group that had an excellent response, and 16 per cent of those who did not seem to be benefited at all.

Although our purpose was to ascertain whether purified scarlet fever antitoxin caused as many reactions as did the serums or antitoxins used previously, attention was also paid to the number of complications, etc., and a careful record was kept. It was particularly interesting to note that such complications were no greater in number and probably fewer

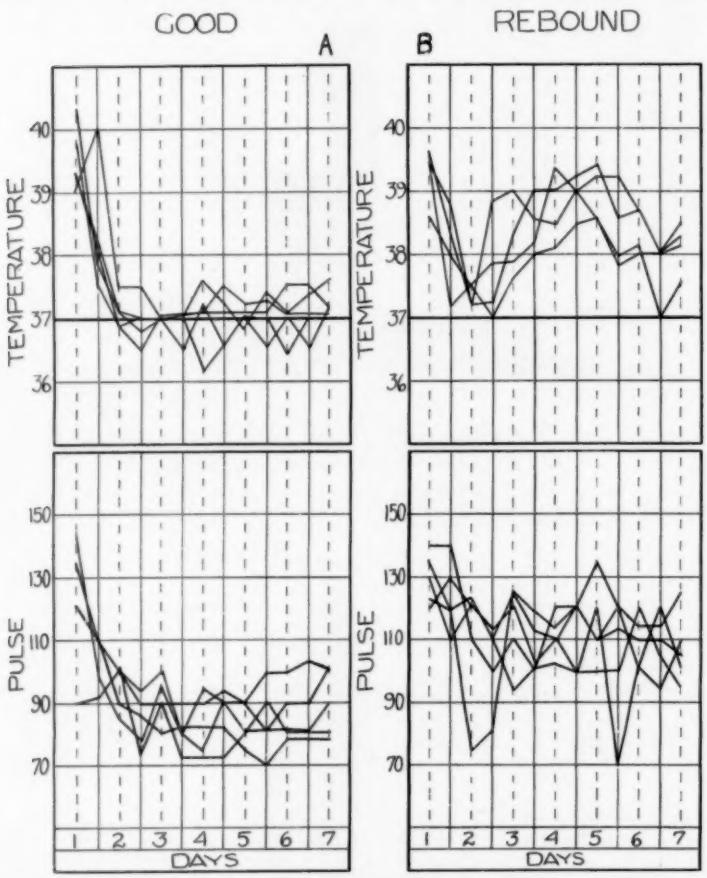

Chart 3.—*A*, the type of reaction seen in 86 of 524 cases is shown. One hundred and fifty-nine patients also showed comparable improvement, although the curve of the drop in temperature was a little more prolonged. These accounted for 46.7 per cent of the cases.

B, many of those patients who did not seem to be benefited had sharp drops after antitoxin administration as indicated and then had a rebound in temperature. Perhaps a second dose would have prevented this.

than these seen in past years. This, however, could not be definitely attributed to the antitoxin since comparable untreated controls were not included in this series. It might well have been that the complication rate of an untreated group might not be much higher.

Many patients ill with scarlet fever who were given antitoxin need not have received it since they were not very sick on admission to the hospital. Other patients seemed to have been moderately benefited. Among this group were individuals who had a slight rise in temperature, from 38° C. to 39° C., an increase which rapidly came down within a few days. Still other cases, toxic and with high temperatures, had remarkable beneficial results. Temperatures as high as 40° C. often

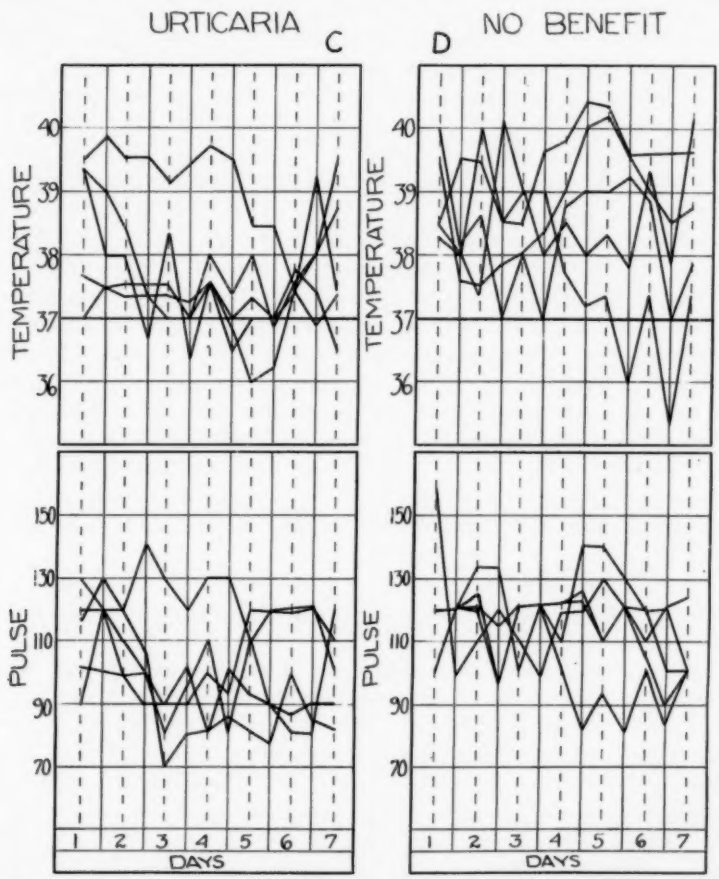

Chart 4.—*C*, that urticaria may send the temperature up is seen from the graphs of these cases. These patients were included in the "no benefit" group. Here temperature readings are charted from the time that serum sickness started.

D, here are illustated the typical "no benefit" cases that are different from types *B* and *C*. Types *B*, *C* and *D* accounted for 150, or 28.7 per cent, of the cases.

came down abruptly to normal within from twelve to twenty-four hours. Yet another group of cases did not seem to have benefited at all.

Of the 524 patients who were treated with antitoxin I, 117, or 22.3 per cent, were not ill on admission so that nothing could be said about beneficial effects in this group. One hundred and fifty-nine, or 30.3 per cent,

were moderately benefited; 86, or 16.4 per cent, had excellent results; 150, or 28.7 per cent, had little or no benefit; 12, or 2.3 per cent, not included among the latter patients, died. If those patients who were not ill on admission were omitted, there would be 407 cases: 159, or 39 per cent of which showed fair results, 86, or 21 per cent, good results; and 150, or 37 per cent, no benefit, while 12, or 3 per cent, died. In brief, 60 per cent of the 407 patients showed some demonstrable benefit. It must be mentioned that our report is based upon the results that occurred after the use of one therapeutic dose of serum. What might have occurred had we used more serum is merely conjectural.

Four hundred and thirty-eight patients, or 83.6 per cent, had no complications, while 86, or 16.4 per cent, did. The types and percentages of the chief complications are tabulated in Tables III and IV. The patient was not always admitted during the first few days of the disease (Table II). It can be seen from Table IV that 356, or 67.9 per cent, of the cases received antitoxin during the first four days, but the complication rate of 15.2 per cent was roughly comparable to the 19.1 per cent in the group of 168 cases treated after the fourth day of the disease. Since there were no untreated controls, no comparisons can be made with treated cases. Attention might be directed to a previous study where there were 39.2 per cent complications in the treated and 36.6 per cent in the untreated group.[1] From these figures, it might be inferentially drawn that we are probably having a milder disease with a decreased reaction rate at the present time. In the absence of untreated controls, however, no credit can be given to the decreased complication rate since the statistics of one year's epidemic cannot be compared with that of another.

Table III reveals that most of the complications are the same as those seen in previous epidemics—otitis media, mastoiditis, cervical adenitis, erysipelas, nephritis, etc.

One hundred and seventeen of the 524 patients need not have been treated with antitoxin since they were not very ill on admission to the hospital. It may be stated, however, that such patients may be given antitoxin since they may develop complications later if not treated. Such conclusions are not logical in light of the fact that our epidemic of scarlet fever, even though the mortality rate was the same, was the mildest we had in years. The death rate of 2.3 per cent does not mean much when it is understood that we receive all the severely ill patients in the community. The important thing is that the total mortality rate of the city has not increased. The mortality rates for Cleveland for 1933, 1934, 1935, 1936, and 1937 (first ten months) were 0.7 per cent, 0.8 per cent, 1.2 per cent, 0.9 per cent, and 0.8 per cent, respectively.

ANTITOXIN II

Ninety-two patients were given this antitoxin, which had been concentrated down to approximately 1.5 c.c. to 2 c.c. Forty-seven patients were

TABLE II

%			DAYS 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	TOTAL CASES 1ST–4TH DAY	TOTAL CASES 5TH DAY OR LATER
	GROUP I: 117 cases not ill on	a	ad	m	iss	to	n																											
55.0	64 uneventful course	a	1	8	11	15	10	12	4	1	1		1																				35	29
7.7	9 with good course	a		3			4	1		1																							3	6
6.0	7 with serum reactions	a		1	1	4	1																										6	1
19.7	23 with fair course	a		1	8	5	2	4	2	1																							14	9
6.0	7 developed complications	a	1		2	2	1		1																								5	2
		b						2			1				1			1						1						1			0	7
6.0	7 showed no benefit	a	1		1	1	1	2				1																					3	4
	GROUP II: 159 cases—resp	on	se	to	a	nt	it	ox	in	ju	dg	ed	as	fa	ir																			
54.8	87 uneventful	a	6	21	22	16	14	3	3	1	1																						65	22
	6 fair course with slight temperature rebound	a	1	2		1		1	1																								4	2
		b										1													1								0	2
19.0	30 had complications on admission	a	3	5	6	10	3	1	2																								24	6
	9 fair, but slight temperature			3	1	3		1	1																								7	2
	relapse	b			1			1				1																					1	2
12.6	20 fair, but developed complications	a	2	5	4	1	3	1	3		1																						12	8
		b							1	1	1	1		1	2						3			1		1	1	1			1	1	0	16
10.7	17 developed serum reactions	a	2	3	3	5	1	2		1																							13	4
	GROUP III: 86 cases in whi	ch	t	he	re	sp	on	se	to	a	nt	it	ox	in	w	as	g	oo	d														
62.8	54 good response	a		12	19	13	5	2	2	1																							44	10
10.2	9 developed complications	a	1	2	2	3	1																										8	1
		b								1		2					1				1	1											0	6
15.5	13 good even with coryza present on admission	a	1	6	3	1	2																										11	2
9.3	8 had serum reactions	a		3	2	1	2																										6	2
2.3	3 had temperature rebound after initial good response	a				1	1	1																			1		1	2		2	2	1
	GROUP IV: 150 cases were	ju	dg	ed	a	s		no		b	en	efi	t																					
39.4	59 no complications	a	4	15	10	11	5	6			6	2																					40	19
32.0	48 developed complications	a	2	7	11	14	5	4	2	2																							34	14
		b				1		5	3	4	1	4		2			2			1	1	2	2			1		1	2		2		1	33
16.0	24 had serum reactions	a	1	3	7	2	5	5	1																								13	11
18.7	28 had complications on admission	a	1	3	6	4	5	2	5							1																1	14	14

a=day of disease on admission—corresponds to time serum was given
b=day of disease that complications appeared

TABLE III

TYPES OF COMPLICATIONS DEVELOPING AFTER SERUM WAS GIVEN

TYPE OF COMPLICATION	DAY OF DISEASE ON WHICH SERUM WAS GIVEN													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14+
1. No complication 438 cases—83.6%	22	91	100	89	59	38	19	12	5	1	1			1
2. With complications	6	11	16	21	10	7	6	2	1	1			2	3
86 cases—16.4%	15.2%				19.1%									
3. Died	1		2		2	1	2			1			1	1 (19th)
12 cases—2.3%	3 = 1.2%				9 = 5.4%									1 (†)
4. Cervical adenitis 24 cases—4.6%	1	5	2	9	2	1	3	1						
1—0.19% (suppurative)	4.8%				1		4.8%							
5. Axillary adenitis						1								
1—0.19% (suppurative)					0.6%									
6a. Catarrhal otitis media	1	1	2	4	2		1							
11 cases—2.1%	2.2%				1.8%									
6b. Suppurative	3	3	6	4	4	1			1					
22 cases—4.2%	4.5%				3.6%									
7. Acute mastoiditis				1		1								
2 cases—0.38%	0.3%				0.6%									

TABLE III—CONT'D

| | | |

TABLE IV

COMPLICATION PERCENTAGE TABULATED WITH RESPECT TO DAY ON WHICH SERUM WAS GIVEN

DAY OF DISEASE SERUM WAS GIVEN	TOTAL CASES TREATED		NUMBER OF CASES DEVELOPING COMPLICATIONS		PER CENT OF CASES DEVELOPING COMPLICATIONS
1	67.9% = 356	28	6	54 = 15.2%	21.4
2		102	11		10.8
3		116	16		13.8
4		110	21		19.1
5	32.1% = 168	69	10	32 = 19.1%	14.5
6		45	7		15.6
7		25	6		24.0
8		14	2		14.3
9		6	1		16.7
10		2	1		50.0
11		1	0		0.0
13		2	2		100.0
14		1	0		0.0
19		1	1		100.0
32		1	1		100.0
?		1	1		100.0
Total		524	86		

benefited, 8 of whom had relapses. Forty-five patients were not benefited at all. Six patients had immediate serum reactions, and 15 had late serum reactions, making a total of 21, or a serum reaction rate of 22.8 per cent. It was the distinct impression that this antitoxin was not so potent as antitoxin I, nor were the reacting elements removed so completely as in antitoxin I. We learned by experience that it took two ampoules of this material to bring about the same clinical effect as that obtained with one ampoule of antitoxin I. One patient treated with antitoxin II died.

ANTITOXIN III

Antitoxin III was concentrated down to approximately 3.2 c.c. to 3.3 c.c. It was a new antitoxin produced, but not marketed, and was tried out in only 30 cases. The serum reaction rate was approximately the same as with antitoxin I. The scarlet fever patients in whom it was used were moderately and severely ill. The clinical betterment was the same as that which followed the use of antitoxin I. Further reports on this antitoxin will follow.

CONCLUSION

In the treatment of 922 cases of scarlet fever with three different kinds of recently prepared concentrated and refined scarlet fever antitoxins, it was found that the serum reaction rate following the administration of two of them was decidedly decreased as compared with the high serum reaction rate following the use of the old type of scarlet fever antitoxins.

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ADRENAL SYMPATHICOBLASTOMA IN CHILDREN

With Special Reference to the Biopsy of Sternal Marrow and of Metastatic Nodule in the Skull

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ADRENAL sympathicoblastoma (synonymously designated in the literature as neuroblastoma, sympathogonioma or sympathoblastoma), though readily recognizable when typical symptoms are present, offers certain difficulties in clearly differentiating it clinically from other malignant neoplastic diseases, particularly from chloroleukemia, acute leukemia, and lymphosarcoma. This disease has been studied extensively because of its striking clinical picture and unique pathologic findings, but no author has thus far given any detailed account of the type cell (sympathicoblast or sympathetic neuroblast) as seen in smears and touch preparations of biopsy material. Such materials, when freshly prepared and stained by any routine hematologic method, reveal certain important morphologic features of the malignant cells, and furnish definite cytologic criteria for correctly disagnosing the disease during life.

Recently a fairly typical case of sympathicoblastoma (Hutchison type) occurring in a young child afforded the present authors an opportunity for studying the morphology of the type cells in tissues obtained by sternal marrow and lymph node punctures, as well as by biopsy of a metastatic nodule in the skull. The following case report, accompanied by complete clinical, hematologic and pathologic data, is concerned mainly with this aspect of histopathology, with particular reference to identification and comparison of the neuroblasts as seen in various tissues studied.

A review of the literature establishes sympathicoblastoma as originating in the adrenal glands and as occurring frequently in infants and children. Under the title, "Cancer of the Adrenal Glands," Frew (1910) reported a series of 51 cases of neuroblastoma including several cases taken from the literature. Of this number, 31 were in infants and children distributed almost equally between males and females, and between Hutchison and Pepper types. Scott, Oliver and Oliver (1933), in a comprehensive review of the literature on adrenal tumors (1880-1932), listed a total of 158 cases, to which they added 4 cases of their own. A perusal of their tables reveals evidence that certain of their cases were ganglioneuroma rather than neuroblastoma, while a few

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others are too incomplete in essential data for positive classification. Excluding all these doubtful cases, together with those occurring in adults and in patients whose age is not stated, there still remain 95 cases of adrenal neuroblastoma occurring in young subjects. The distribution as to sexes and types is again somewhat similar to that observed earlier by Frew. Since 1932, a total of 53 additional cases of sympathicoblastoma in children have been published. Table I summarizes the salient points of all these cases.

TABLE I

SUMMARY OF 53 CASES OF ADRENAL NEUROBLASTOMA IN CHILDREN (LITERATURE REVIEW FROM 1932 TO 1937)

	HUTCHISON TYPE	PEPPER TYPE	MIXED TYPE	UNCERTAIN	TOTAL
Site of primary tumor:					
(1) Right adrenal	6	4	2	5	17
(2) Left adrenal	9	6	0	3	18
(3) Both adrenals	1	2	0	0	3
(4) Not stated	10	1	0	4	15
Total	26	13	2	12	53
Sex incidence:					
(1) Male	17	8	1	6	32
(2) Female	9	4	1	6	20
(3) Not stated	0	1	0	0	1
Total	26	13	2	12	53
Average age of patient (years)	5	2.1	5.6	4.3	
Average duration of symptoms (months)	5.3	3.2	1.6	4.6	

A general summary of 179 cases of adrenal neuroblastoma occurring in children recorded in the literature up to the time of writing, and incorporating all the data from these three reviews, is given in Table II. In tabulating the cases, and unless otherwise clearly stated, the authors

TABLE II

GENERAL SUMMARY OF 179 CASES OF ADRENAL NEUROBLASTOMA IN CHILDREN (LITERATURE REVIEW FROM 1880 TO 1937)

	HUTCHISON TYPE	PEPPER TYPE	MIXED TYPE	UNCERTAIN	TOTAL
Primary site of tumor:					
(1) Right adrenal	27	26	2	17	72
(2) Left adrenal	32	17	0	15	64
(3) Both adrenals	2	10	0	2	14
(4) Not stated	15	4	0	10	29
Total	76	57	2	44	179
Sex incidence:					
(1) Male	44	28	1	20	93
(2) Female	28	24	1	20	73
(3) Not stated	4	5	0	4	13
Total	76	57	2	44	179
Average age of patient (years)	3.9	1.7	5.6	3.1	
Average duration of symptoms (months)	5	3.6	1.6	5.1	

have attempted, in conformity with the data available, to classify them either as Hutchison or Pepper type. Unfortunately, in many instances autopsy studies were unavailable, and the information otherwise provided lacked essential details. Consequently, classification of such cases was impossible. In general, the usable cases were classified on the basis of the major metastatic involvement of the liver (Pepper type) or of the skull (Hutchison type); the few cases that were demonstrated by autopsy to have some involvement of the liver and also of the bone marrow, but in which the skull was free from metastasis, have been grouped as "mixed" in type. The average duration of symptoms was computed as being the length of time elapsing from the initial appearance of the first clinical manifestations until the time of the patient's death.

REPORT OF CASE

H. B., a two-and-one-half-year-old male child, was brought to the Bobs Roberts Memorial Hospital (Nov. 19, 1936), because of a bluish discoloration about the eyes which had first appeared three weeks previously. The family history was entirely negative; birth at full term was normal with no neonatal complications, and subsequent development had been satisfactory. Except for a few upper respiratory infections the patient had no past history of illness. The previous year he had been inoculated against diphtheria.

Present Illness.—The mother had noticed a reddish blue area about the left eye three weeks before the patient was seen in the clinic. There was no known history of trauma. The discoloration had progressed appreciably for about ten days when a similar discoloration appeared about the right eye. Then for the first time the mother noticed the pallor of the child's skin. During the week prior to admission the child's appetite began to decline.

Physical Examination.—The patient was a fairly well-nourished, well-developed male child with a waxy pallor. He was irritable but seemingly not acutely ill. On closer inspection, however, the superficial veins of the forehead and temporal region were seen to be moderately prominent. Around both orbits, distinct areas of ecchymosis were seen, but no exophthalmos was present and the fundi were quite normal. The cervical lymph nodes were moderately enlarged. Nose and throat examination was negative. The lungs were normal; the heart, with a moderately loud systolic murmur at the apex, was not enlarged. The liver was palpable at about 2 cm. below the costal margin, but no other abdominal masses were noted. Neurologic examination disclosed no unusual signs.

Roentgenographic Examination.—The skull plate showed questionable slight diastasis of the longitudinal suture and a granular pattern in the parietal bones and normal orbits. The chest film revealed the lungs as clear except for a slight generalized "graying" which was interpreted by the roentgenologist as resulting from shallow respiration at the time of examination. The heart was normal both as to size and contour. In the extremities the trabeculae at the ends of the humerus, the radius, and the ulna were slightly accentuated.

Laboratory Findings.—The blood count on admission showed 2,200,000 erythrocytes, 5.9 gm. per cent hemoglobin (Newcomer), 10,500 leucocytes, 20,000 platelets, and 21 per cent packed cell volume. A fragility test placed the initial hemolysis at 0.46 per cent and the complete hemolysis at 0.34 per cent sodium chloride solution. The sedimentation rate (Laudau's micromethod) was 46; coagulation time (Lee and White) 5 minutes; prothrombin time (Howell) 10 minutes; and clot retraction, though present, was delayed. The complete hematologic data are given in Table III.

TABLE III

SUMMARY OF BLOOD EXAMINATIONS

DATE	R.B.C.	HB. GM. %	W.B.C.	PLATE-LETS	L	P	M	E	B	IMM. MYEL.	PL.	NUC. R.B.C.
11/19/36	2.20	5.9	10,500	20,000	40	27	8	4	0	9	2	2
11/23/36	2.50	6.3	8,500	80,000	39	25	10	4	1	20	1	1
12/ 7/36	2.41	6.3	8,700	80,000	48	22	3	1	1	16	9	1
12/11/36	3.38	7.9	9,900	50,000	47	28	5	5	0	15	0	3
12/18/36	1.54	4.2	10,500	40,000	34	41	7	1	1	16	0	8
12/21/36	1.28	3.5	11,300	40,000	22	57	6	2	0	13	0	3
12/24/36	1.47	3.4	6,000	20,000	32	51	5	0	0	12	0	4
12/26/36	1.28	2.9	5,700	30,000	32	51	8	1	0	7	0	2
1/ 4/37	.96	2.5	8,000	60,000	33	40	11	1	1	14	0	0

Note: Abbreviations for differential counts are as follows: L (lymphocytes), P (neutrophiles), M (monocytes), E (eosinophiles), B (basophiles), Imm. Myel. (immature myeloid cells, including myeloblasts, myelocytes and metamyelocytes), Pl. (plasma cells), and Nuc. R.b.c. (nucleated red blood cells). Hemoglobin is expressed in grams per 100 c.c. of blood according to the Newcomer method. Five blood transfusions were given as follows: 11/23/36 (150 c.c.), 11/24/36 (125 c.c.), 12/8/36 (150 c.c.), 12/9/36 (100 c.c.), and 12/29/36 (250 c.c.).

Fig. 1.—Appearance of the patient (Dec. 24, 1936), exhibiting bilateral exophthalmos with ecchymoses of eyelids and a large metastatic nodule over the left temporal region.

The urine was entirely normal. Tuberculin (Mantoux), Wassermann and Kahn tests were all negative.

Clinical Course.—The initial diagnosis was "probable early leukemia," although adrenal neuroblastoma and osteogenic sarcoma were also considered. Two blood transfusions of 150 c.c. each, given on the first and sixth days after admission, slightly improved the patient's general condition. At no time was the temperature elevated. On the eleventh day of hospitalization a swelling was noticed over the left temporal region. Several days later, at the request of the parents, the child was discharged.

Second Admission.—One week after being discharged the patient was readmitted (Dec. 7, 1936) because of increasing pallor, weakness, and apparently progressive development of his illness. The hemorrhage about the orbits had become accentuated, and a mild exophthalmos of the left eye was noticeable, with choking of the nerve head on that side. The mass over the left occipitoparietal region had now become decidedly enlarged. The liver had likewise increased in size until it extended 5 cm. below the costal margin, but the spleen was still impalpable and the abdomen free of any other discernible mass. In spite of several blood transfusions during the week following the second admission the child's condition became progressively worse. Both eyes became protuberant, and several new nodules appeared about the skull (Fig. 1).

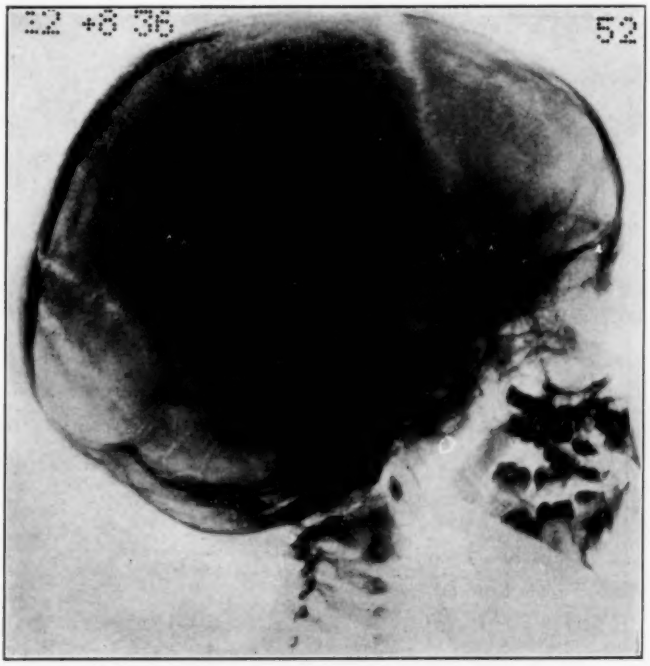

Fig. 2.—Roentgenogram of the skull, revealing diastasis of the cranial sutures and slightly granular appearance of the posterior portion of the parietal bone.

Roentgenographic examination at this time revealed a definite increase in the diastasis of the sutures but no further changes in the appearance of the long bones. The "graying" previously noted in the lungs was now very definitely increased, and identified as accentuated markings of the bronchovascular trunk (Figs. 2 and 3).

Sternal Marrow and Lymph Node Punctures.—The first sternal marrow puncture was made on Dec. 11, 1936, and a small amount of the aspirated marrow tissue studied. In a stained smear of this material, in addition to the usual marrow cells which were definitely decreased in number with a relative increase in erythrogenic elements, were clusters of unusually immature cells relatively large in dimensions and forming syncytial masses simulating a mosaic pattern (Fig. 4A). The boundaries of neighboring cells forming the syncytium were indistinct in many

places. The cytoplasm of these pathologic cells was as a rule scant in amount and irregularly granular, taking a bluish gray hue with May-Grünwald-Giemsa combination stain. The fluid nature of the protoplasm was apparent on the stained smears, as many of these cells were extremely variable in configurations. The nuclei were relatively large with uniformly granular chromatin pattern taking a deep purple tint, and in addition contained numerous scattered larger granules of heavily staining chromatin deposits. Nucleoli, though present in a few cells, were for the most part not visible, probably because of the heavy staining of the nuclear chromatin. A moderate number of these cells contained mitotic figures.

Smears made from material aspirated from an enlarged cervical lymph gland also revealed the presence of a large number of pathologic cells morphologically identical with those found in the sternal marrow smears.

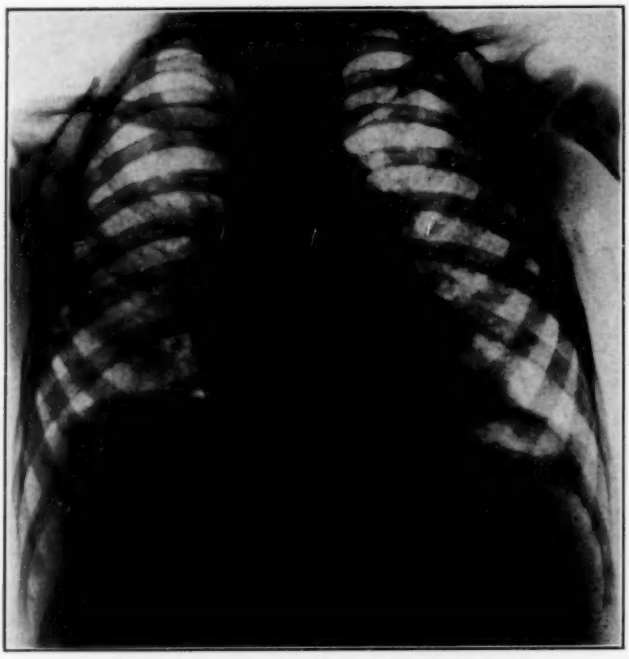

Fig. 3.—Roentgenogram of the chest, showing accentuated bronchovascular markings with a suggestion of slight stippling throughout the lung fields.

Sections of material obtained by biopsy (Dec. 15, 1936) of one of the tumor masses in the skull contained both large and small clumps of tumor tissue composed of large, rounded, spindle-shaped and oval cells with scant cytoplasm and having large finely stippled nuclei. This biopsy pointed to the diagnosis of round cell sarcoma.

Several touch or imprint preparations made from the cut surface of one of the biopsy tissues, stained by the May-Grünwald-Giemsa method, also revealed cells having the identical morphologic characteristics of the pathologic cells (Fig. 4B).

On the basis of this diagnosis, deep x-ray therapy was instituted but with no apparent beneficial effect, the child becoming progressively stuporous, and anorexia more extreme. On several occasions large amounts of food were vomited. The tumor masses on the skull continued to enlarge, accompanied by progressive pro-

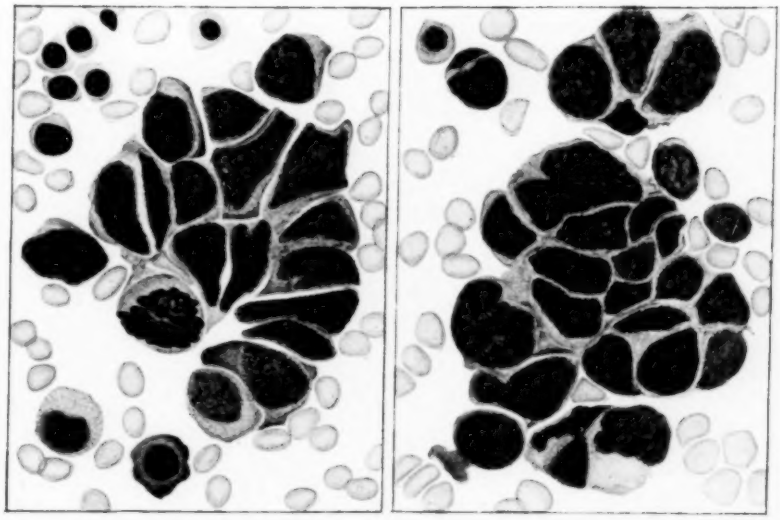

Fig. 4-A. Fig. 4-B.

Fig. 4.—Camera lucida drawing of malignant cells. *A*, a cluster of sympathicoblasts arranged in mosaic pattern as seen in a smear of sternal marrow material; *B*, similarly arranged aggregation of immature neuroblasts as observed in an imprint preparation of a metastatic nodule in the skull. (May-Grünwald-Giemsa stain, oil immersion lens, ocular × 10.)

trusion of both eyeballs, and the superficial veins of the face and skull became highly prominent. The anemia progressed so rapidly that shortly before death the red cell count was only 960,000 and hemoglobin 2.5 gm. per cent. The child expired on the twenty-eighth hospital day (Jan. 4, 1937).

Autopsy Protocol.—The post-mortem examination, conducted by Dr. Charles Dunlap, one and a half hours after death, established the following anatomic diagnosis: (1) Hutchison's tumor (neuroblastoma) of right adrenal gland with metastases in the regional lymph nodes, the periaortic lymph nodes, inguinal nodes, lungs, liver, peribronchial nodes, skull bones and in the petrosal portion of both temporal bones. (2) Tumor erosion and bony proliferation of the inner table of the skull. (3) Diastasis of the cranial sutures. (4) Subperiosteal hemorrhages of ribs. (5) Fatty degeneration of liver, kidneys, and myocardium. (6) Cloudy swelling of both kidneys. (7) Marked generalized anemia. (8) Fatty infiltration and anemia of myocardium. (9) Patent foramen ovale. (10) Subcutaneous hemorrhage of the face and scalp. (11) Edema of the face. (12) Corneal perforation of the left eye. (13) Retrocecal appendix.

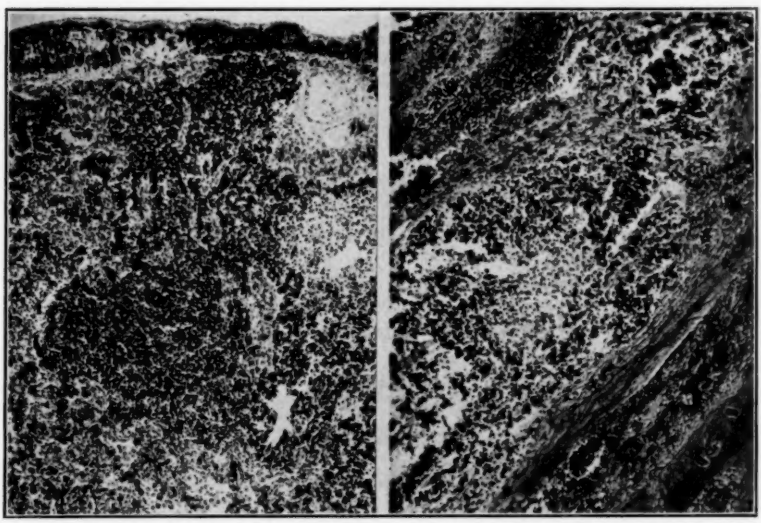

Fig. 5. Fig. 6.

Fig. 5.—Photomicrograph of a section of lung, visualizing an extensively infiltrated area just beneath the visceral pleura (magnification × 125).

Fig. 6.—Photomicrograph of a section of rib marrow, containing diffuse metastasis (magnification × 125).

The tumor mass in the region of the right kidney, measuring 8 by 5 cm., presented an irregularly lobulated surface overlaid by superficial hemorrhage. The mass, continuous with the enlarged lymph nodes about the aorta, when opened revealed the kidney to be intact and normal in shape although only about two-thirds the size of the opposite kidney. The right kidney was seated at the bottom of the tumor mass and formed the tumor's lower pole and lower lateral surface. The cut surface of the tumor presented irregular nodules of soft red hemorrhagic tissue and in the central portion of the tumor were two irregular nodules, 2 and 1 cm. in diameter, composed of light grayish brown tissue suggesting adrenal medulla. Fibrous strands and blood vessels were arrayed throughout the tumor and the entire mass weighed 260 gm.

Evidence of metastases into the skull was abundant when the scalp was reflected exposing gross hemorrhage which involved the subcutaneous tissues over the frontal, parietal, temporal and occipital bones. The inner table of the calvarium was diffusely ragged and spongy, with an erosion penetrating the skull at the anterior portion. A mass of hyperplastic skull bone over the left parietal region was composed of innumerable easily broken spicules grown down towards the dura and imparting a spongelike appearance to the inner surface of the calvarium.

When the dura was reflected, its convolutions were seen to be considerably flattened. Tumor tissue had invaded the interior wall of the two sigmoid sinuses adjacent to the petrosal portion of the temporal bones. When the dura was separated from the base of the skull, the entire lower left temporal region of the skull was found to be composed of spongy, friable, dark red bone so soft that part of it came away with the dura. This process also involved the posterolateral surface of the left orbit.

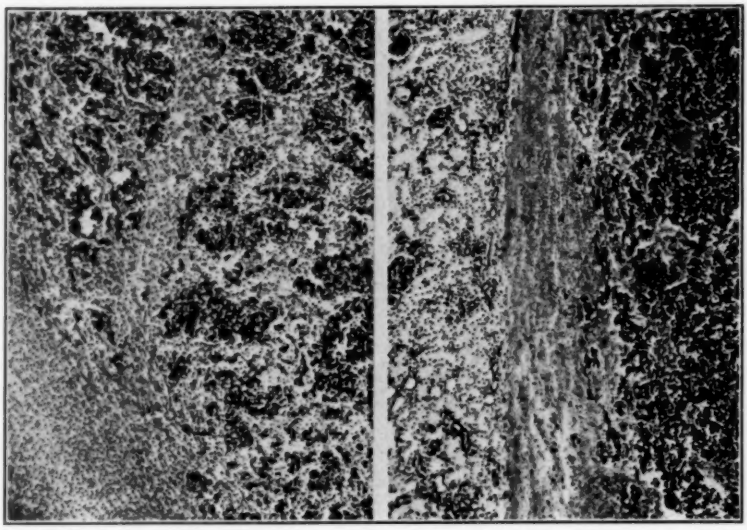

Fig. 7. Fig. 8.

Fig. 7.—Photomicrograph of a section of liver demonstrating ball-like aggregations of pathologic cells with compression of hepatic cords (magnification × 125).

Fig. 8.—Photomicrograph of the primary tumor mass (at the right) adjacent to the renal parenchyma (at the left), separated by a hemorrhagic layer (magnification × 125).

When the left orbit was opened, the bony wall was found to be soft, dark red, spongy, and firmly adherent to the orbital fat, with hemorrhage into the superficial layer of the fat. The mastoid cells were filled with mucus, blood, and tumor tissue.

Histologic examination of sections prepared from various tissues of this patient disclosed widespread metastases of tumor cells both round and oval, relatively small in size with deeply pyknotic nuclei and exhibiting little stroma formation. The marrow of the vertebra, calvarium, and rib were extensively replaced by the tumor tissue (Fig. 6). In the lung, tumor cells were profusely growing in blood vessels, lymphatics, and in alveolar walls, and invading the bronchial walls, partly destroying the cartilage and causing much hemorrhage (Fig. 5). The liver contained numerous tumor cells clustered roughly in polypoid distribution on the rem-

nants of partially destroyed structure (Fig. 7). Small groups of tumor cells were growing in the sinusoids of every lobule. Central necrosis and fatty degeneration were outstanding. The lymph nodes were almost completely replaced by tumor tissue and fibrous bands had here and there walled off the tumor cells into irregular, round groups. The right kidney revealed a few small metastases in the tubules, and the organ lay in contact with a large tumor mass that had not directly invaded the parenchyma (Fig. 8). The left kidney gave no evidence of metastases. Fat and fibrous tissue from the orbit were largely replaced by tumor tissue and gave evidence of old hemorrhage.*

COMMENT

The histopathology of adrenal sympathicoblastoma has been so well delineated that any additional description is superfluous. It is only necessary to recall that the type cell is now conceded to be an embryonal nerve cell derived from the neural ectoderm and represents the primary sympathetic cell, sometimes known as the sympathogonion of Poll (1905). Bailey and Cushing (1926) speak of sympathicoblasts, a group of undifferentiated pluripotential cells derived from the ganglion crest, which migrate into the visceral areas to form the anlage of the sympathetic nervous system and finally differentiate into unipolar and multipolar neuroblasts. The first clear differentiation of malignant tumors, composed of primitive nerve elements, into (1) neurocytoma and (2) neuroblastoma began with the work of Wright (1910), while a classification based on the structural differences (sympathoblastoma, ganglioneuroblastoma, ganglioparaganglioneuroblastoma, ganglioglioneuroblastoma) was suggested by Robertson (1915). The histologic observations

*Since writing this paper another typical case of adrenal sympathicoblastoma (Hutchison type) has been observed in the Bobs Roberts Memorial Hospital:

D. T., a white female child, 2 years and 3 months old, was first seen in the Outpatient Clinic with the complaint of a swelling of the left jaw, which had first appeared three weeks previously and which was followed a few days later by swelling of the legs and abdomen. The child had some difficulty in urination, but at no time was fever ever noted. The family and developmental histories were entirely negative, and except for frequent colds the patient previously had never been ill.

Physical examination on admission revealed a normally developed child with a firm and nonfluctuant swelling over the left mandible and cheek, extending from the preauricular region down to the point opposite the canine teeth. The mass was readily seen both from within and without the mouth cavity. There were also several enlarged cervical lymph nodes on both sides. The tonsils were slightly enlarged, but no injection was noted either of the tonsils or of the pharyngeal mucous membrane. Heart and lungs were normal. The abdomen was greatly protuberant, with an enlarged liver reaching nearly 10 cm. below the costal margin in the midclavicular line. Further to the left side of the abdomen, under the rib margin, was a hard, irregular mass which did not move with respiration.

Laboratory findings were as follows: The red cell count varied from 2.60 to 4.30 millions, with hemoglobin from 52 to 76 per cent; leucocytes numbered from 4,950 to 10,400. The differential count of leucocytes upon admission showed 83 per cent neutrophiles, 13 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophiles. Occasional myelocytes and plasma cells were also seen. Sedimentation rate was 45 per cent. Urinalysis was negative. Roentgenographic examination revealed a pathologic fracture through an osteolytic lesion in the posterior portion of the ramus of the left mandible, together with coarse round osteoporosis in the lower ends of the femoral shaft and slight but definite stripping up of the periosteum with deposition of the bone beneath. The right lung field showed infiltrative lesions which were interpreted as being metastatic in nature.

Biopsy of a small piece of vascular tumor tissue removed from the left mucobuccal fold revealed upon sectioning a mass containing densely packed hyperchromatic round cells exhibiting an extreme degree of mitotic division. The diagnosis of neuroblastoma was made by Dr. H. G. Wells.

Sternal marrow puncture established the presence of small aggregations of neuroblasts, identical with those seen in the first case.

In spite of one blood transfusion and eight x-ray treatments the patient died two and one-half months after admission.

Autopsy (Dr. P. R. Cannon) disclosed extensive adrenal neuroblastoma, originating in the right adrenal gland and with widespread metastases in the liver, retroperitoneal lymph nodes, and numerous bones, including the cranium and around the orbit.

of Wright (1910) emphasize the association of the undifferentiated nerve cells with delicate fibrils which, by Mallory's method, stain like neither neuroglia, collagen nor fibroglia fibrils, and which closely resemble those occurring in the anlage of the sympathetic nervous system. Wiesel (1905) previously demonstrated that early in the developmental process the primitive cells of the sympathetic nervous system (the so-called embryonic formative cells) invade the cortical anlage of the adrenal glands, resulting in the formation of the medulla of the organs. These cells may lie dormant in the medullary portion of the gland for varying lengths of time, or may at any time give rise to proliferative changes. This clearly explains the medullary origin of adrenal neuroblastoma, although the primary origin elsewhere is likewise accounted for by the presence of the undifferentiated formative cells of the sympathetic nervous system wherever such anatomic elements naturally occur. The multiple presence of tumor growths in various organs and tissues of the body may also be explained by the ubiquitous occurrence of the sympathicoblasts (sympathogonia) as well as by metastasis, to which neuroblastoma is particularly disposed.

In the present case the aspirated material from the sternal marrow contained numerous clusters of relatively large immature cells answering the commonly depicted cytologic characteristics of sympathicoblasts, but with no definite evidence of fibrils. These cells occurred in clumps composed of varying numbers of primitive cells characterized by relatively large nuclei rich in chromatin but scant in flexible cytoplasm. No definite fibrils were seen, although frequently the distinctly fluid protoplasm tended to be precipitated as fine strands. While occasionally granular in appearance, the cytoplasm was for the most part rather uniform and here and there contained vacuoles. With Giemsa solution the nuclear chromatin stained a deep purple. No nucleoli were definitely discernible. Some of these cells were round, but the majority were polygonal, one cell lying in such close contact with another that in the aggregate they presented a veritable mosaic picture, in some instances assuming a syncytial arrangement, particularly in areas of ill-defined cell boundaries. In histologic sections made from autopsy materials, the neuroblasts, both as described in the literature and as found in the present case, were rather small in size; but in stained smears of biopsy materials the pathologic cells, as compared with the blood cells, were mostly of large dimensions, only a few being as small as lymphocytes. Apparently no rule obtains as to cell dimensions, the variations in some cases being pronounced.

The aspirated material from an enlarged lymph node in the left side of the neck contained primitive sympathetic neuroblasts quite similar to those found in the sternal marrow, which finding constitutes definite evidence of the involvement of the lymph glands by metastasis. The

cytologic characteristics of these malignant cells in the lymph node are essentially identical with those in the material obtained by sternal puncture.

Grossly the metastatic tumor mass obtained by biopsy from the parietal region of the skull appeared hemorrhagic. When touch preparations made from the cut surface of the removed mass were stained by the May-Grünwald-Giemsa combination method, cells similar to those seen in the sternal marrow and lymph gland were again demonstrated. Preparations from the tumor mass itself, however, contained even greater numbers of extremely large cells, each with two or more nuclei. While mitotic figures were fairly numerous, the presence of two or three nuclei in large pathologic cells may be interpreted as signifying direct cell cleavage, which in turn may explain the mosaic formation. At any rate, without question the identification of these cells as neuroblasts establishes a metastatic involvement of the cranial bones.

When stained by the same method as employed in the study of biopsy materials, similar imprint preparations from the tumor masses found at autopsy in the suprarenal gland as well as in all other organs showing metastatic foci, revealed the identical morphologic characteristics observed and described in the foregoing paragraphs.

In this connection, special attention must be directed to the general configuration of these cell clusters as seen in the various preparations of biopsy materials. In the literature, the so-called rosette formation in neuroblastoma is too indiscriminately looked upon as pathognomonic of this type of neoplasm. Accurately speaking, none of the smears or touch preparations studied by the present authors revealed the presence of true rosettes. This finding was confirmed by the histology of the tumor masses obtained at autopsy, no true rosettes having been seen either in the sections or in the touch preparations of the organs involved. The malignant cells exhibited a striking tendency to form aggregations resembling pseudoadenomatous structures. In accordance with the suggestions made by Bailey and Cushing (1926), it would be advisable to restrict the term rosette to the description of a small canal surrounded by primitive nerve cells. The typical ball-like aggregations of cells without a definite central canal, found in the present case in the various preparations of tissues, are not true rosettes but merely the pseudorosettes so characteristic of sympathicoblastoma. As described above, these ball-like aggregations of sympathicoblasts are in general appearance more typically mosaic than rosettes, and should be referred to as such. Incidentally, the formation of mosaics by the malignant cells may be considered as indicative of their cytologic immaturity, clinically coinciding with rapid growth and extreme malignancy; on the other hand, the formation of true rosettes signifies the relative maturity of the tumor cells, clinically characterized by their slow development and mild malignancy.

The present case also demonstrates the typical locations of the secondary metastatic processes of this neoplasm. From the autopsy protocol it is apparent that the metastases were widespread, the major localization occurring in the cranial bones with minor metastases in many other organs and bones. From the general summary of all reported cases of adrenal neuroblastoma (Table II), it is clear that the Hutchison type may arise from the primary focus either in the right or in the left adrenal, although primary origin in the left suprarenal slightly predominated. With the Pepper type the noteworthy feature is the significant predominance of the right primary focus. In the present case the major seat of malignancy was in the right adrenal gland and the site of major metastasis in the cranium. At the same time, however, the liver was definitely enlarged and histologically contained numerous metastatic nodules. That is to say, the classification of adrenal neuroblastoma into Hutchison and Pepper types is necessarily more or less arbitrary in that it is based solely upon the sites of major metastasis. Actually, either type may produce both the skull and liver metastases in varying proportions.

As to the hematologic aspect of adrenal sympathicoblastoma, although throughout the course of the disease this patient had no significant leucocytosis, yet the appearance of immature myeloid cells, particularly the leucoblasts, premyelocytes, and myelocytes, was constant. No malignant cells were ever found at any time in the peripheral blood. The blood platelets were greatly reduced in number, as might very well be expected in a condition where a progressive involvement of the bone marrow is likely to interfere with the normal formation of megakaryocytes. Red blood cell formation was likewise interrupted, causing profound secondary anemia with an occasional appearance of a few normoblasts. This picture, which is quite in keeping with that seen in any malignant neoplastic disease involving the bone marrow, differentiates neuroblastoma from leukemic states, particularly chloroleukemia. In this connection mention must be made of a possible diagnostic dilemma which may confront the clinician if he relies exclusively upon the syncytial masses in the sternal marrow. Recently in a case of acute leukemia with marked hepatic and splenic enlargement and aleukemic blood picture, the sternal marrow smears disclosed a few clusters of immature cells, presumably myeloblasts and closely simulating the neuroblastic syncytium. In such a case, the possibilities are either leukemia or neuroblastoma (Pepper type); hence the diagnosis can only be presumptive and tentative. Leukemia can be positively diagnosed only when either the peripheral blood becomes definitely leukemic or when leukemic infiltrations of organs are finally demonstrated at autopsy, whereas the diagnosis of neuroblastoma can be positively made only at autopsy upon demonstration of the primary neoplasm with secondary metastases.

The differentiation of neuroblastoma from lymphosarcoma is now said to offer little difficulty in as much as the morphologic and histologic characteristics of these two conditions have been well defined. Nevertheless, absolute distinction from the examination of the histologic sections alone may at times be difficult or even impossible, inasmuch as in the present case both the biopsy report and the neurologic diagnoses were "round cell sarcoma" and "probable lymphosarcoma," respectively. In lymphosarcoma, however, the typical picture is one of endless multiplication of the same type of immature lymphocytes invariably occurring first in the lymph nodes, the architecture of which is completely destroyed. In the sympathicoblastoma on the contrary, the lymph glands are involved only by secondary metastasis, there being here also more or less typical alveolar arrangement of malignant cells with mosaic formation.

SUMMARY AND CONCLUSIONS

A case of adrenal sympathicoblastoma (neuroblastoma) occurring in a male child two and a half years old with clinical, hematologic and pathologic data is presented.

Smears made from materials aspirated from both the sternal marrow and a cervical lymph node contained clusters of typical, slightly basophilic cells with relatively large hyperchromatic nuclei and fluidlike cytoplasm which as a rule was scant in amount. These cells, when later compared with the malignant cells similarly demonstrated from the tumor masses, were identified as metastatic sympathicoblasts or neuroblasts from the primary focus in the adrenal glands. Identical cells and groups of cells, but often with two or three nuclei and of larger dimensions, were also found in the imprint preparations made from the cut surface of the metastatic nodule in the skull.

No typical rosette formation of the pathologic cells was seen in any of the preparations studied; instead, the ball-like aggregations of cells described more typically as mosaic patterns were seen. For this reason the general configuration of cell clusters characterizing this type of neoplasm should be referred to as pseudorosettes or preferably mosaics.

While, because of the major localization in the skull, the case here presented is properly classified as being that of Hutchison type of neuroblastoma, there were also numerous metastatic nodules of tumor tissue in the liver, indicating such a classification to be purely arbitrary.

The hematology of adrenal neuroblastoma and its differential diagnosis from chloroleukemia and lymphosarcoma, with which the condition is most frequently confused, are briefly discussed.

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GENERAL HEALTH AT MATURITY OF TONSILLECTOMIZED AND NONTONSILLECTOMIZED CHILDREN

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AN EXTENSIVE investigation by Kaiser has shown that beneficial results do not always follow the removal of tonsils and adenoids. He reports, "Apparent benefits during the first few postoperative years are not so evident over a ten-year period. . . . Acute head colds and otitis media . . . . are not essentially influenced. . . . The respiratory infections such as laryngitis, bronchitis, pneumonia, not only are not benefited, but actually occur more frequently in tonsillectomized children. . . . Recurrent attacks (of rheumatic manifestations) are not benefited at all."[1] The operated cases were compared with control children of like ages and histories who for various reasons did not have their tonsils and adenoids removed as recommended.

Kaiser's study focused attention on the effects of tonsillectomy on illnesses contracted during an extended period of time. This article presents findings on the general health status of operated and nonoperated cases who were examined periodically from childhood to maturity by the Elizabeth McCormick Memorial Fund of Chicago. The group was much smaller than that reported on by Kaiser but is less selective than his since all of them were so-called "well" children and many were said to have healthy tonsils.

The present study is based on white children who were in regular attendance in the public schools of a small industrial city in the Middle West (Joliet, Ill.) whose parents were interested in cooperating in a long-term investigation on growth and development. Four hundred fifteen children were given yearly a thorough physical examination without clothing from the age of eight or nine years to twelve or thirteen years. During this period the parents of these children were regularly advised by health specialists as to the physical needs of their children.

One pediatrician* made 80 per cent of all of the examinations during the years of childhood. The child's parents (one or both) were present at each examination and from them unusually complete histories were obtained. Therefore, the examiner was familiar with the history and in a position to observe conditions over a period of time before passing judgment on the advisability of removing the tonsils and adenoids. However, the families represented had their own personal physicians and in many cases it was on their decisions rather than on that of the examiner that tonsils were removed.

From the Research Department of the Elizabeth McCormick Memorial Fund.
*Dr. S. C. Henn of Chicago.

When these children were approaching their twenty-first birthday they were again given a thorough physical check-up. Two hundred thirty-eight of them were available for this final inventory. At this time each individual was seen by three examiners: an eye, ear, nose, and throat specialist; a dentist; and a general physician.* Blood and urine analyses were made and roentgenograms on the request of any one of the examiners. All records including the histories were carefully gone over by the general physician who made recommendations and summarized the clinical findings in the form of ratings on physical condition.

The boys and girls included in this study represent a wide range in economic conditions. Some of them were from well-to-do families (1923-36) and some were from the lowest economic brackets. On the whole, they are representative of the large middle class of second and third generation American families in the Middle West.

Physically and mentally the group were considered normal, well-developed young people. Body measurements at maturity showed the average boy was 5 feet 9.1 inches tall and weighed 145 pounds; the average girl was 5 feet 3.5 inches tall and weighed 121 pounds. According to psychologic tests they are of "normal" intelligence.

For comparative purposes a group of young people living in the community who were from the same age and socioeconomic levels but who were not under observation during childhood were included in the investigation. Fifty-two boys and 54 girls, most of whom were in their twentieth year, were examined.†

Incidence of tonsillectomy in the groups studied was fairly low, according to surveys from various sections of the country. Tonsils had been removed in 19 per cent of the children before they were eight years old. By twelve years of age 40 per cent had been operated on and by twenty-one years of age 50 per cent. In the group followed from middle childhood, only one out of five reached maturity with tonsils said to be free from clinical symptoms of infection—here called "healthy" tonsils. Among the cases examined first at maturity, the proportion having healthy tonsils was two in eleven or 18 per cent.

General health of most of the children was "fair" to "good" through the childhood years, according to yearly ratings recorded at the time of examination. Comparative results show conclusively that children who did not have their tonsils removed when advised to do so were in poorer all-round condition than those who had the operation. Large differences in health ratings between tonsillectomized children and nonoperated children for whom tonsillectomy was recommended, were consistently noted throughout late childhood and are statistically reliable. However,

*All examiners were from Joliet. Mentioned in the order given above they were respectively: Dr. H. V. Wadsworth; Dr. George W. Young; Dr. Marion K. Bowles (for the girls), and Dr. Lewis Woodruff (for the boys).

†Dr. Lena Stewart examined the girls. Other examiners were the same as previously mentioned.

the physician who advised the tonsillectomy also rated general health at the same time. His judgment of the need for surgical treatment very likely implied other indications of an unsatisfactory physical status. Under these conditions a relation between infected tonsils and relatively poor general condition would be expected. Hence, although the health of children in need of tonsillectomy was unsatisfactory, a causal relation between general health and diseased tonsils has not been established.

Absence of clear-cut evidence of a beneficial effect of removal of tonsils on general health is also shown in the histories of 35 children who were never in a satisfactory physical condition during the period of study. Seventeen of them, or 49 per cent, were advised to have their tonsils removed but did not have the operation; two of them had the operation satisfactorily performed but failed to show improvement; two of them had the tonsils incompletely removed.

Percentages of the groups described as in good, fair, and poor condition at the time of the last examination in childhood and throughout a four-year period of observation are shown in Table I. Results are presented for operated children and nonoperated children who had been advised to have tonsils removed.

TABLE I

GENERAL HEALTH IN CHILDHOOD OF TONSILLECTOMIZED AND NONTONSILLECTOMIZED CHILDREN

GENERAL CONDITION	TONSILS OUT		TONSILS IN
	7 YEARS OR YOUNGER N = 79 PER CENT	8 TO 12 YEARS N = 85 PER CENT	OPERATION ADVISED 8 TO 12 YEARS N = 53 PER CENT
At conclusion of study (Age 12 or 13 yr.)			
Good	88	89	40
Fair	11	10	53
Poor	1	1	7
During period of study (Ages 8 to 12 or 13 yr.)			
Good	52	34	13
Fair-Good	44	58	51
Fair	3	6	28
Poor-Fair	1	2	8

Data on the tonsillectomized children are given according to the age at which tonsils were taken out. When the operation was prior to the study the exact age was not always recorded. However, in the majority of these cases the records show tonsillectomy before or by six years of age.

As previously stated, not all of the children whose tonsils were removed during the period of the study (eight to twelve years) had the operation on the recommendation of the pediatrician who regularly examined them. But, each of the nonoperated cases reported in the table had been definitely and repeatedly advised by him to have the tonsils out.

The age at which tonsils were removed appeared to have little influence on general health in late childhood. At the time of the last examination, when the children were twelve or thirteen years of age, most of the children (88 per cent) were in good or very good condition. Equal proportions of those operated on before and after eight years of age were reported in good health and the same proportion of each age-group was in poor general condition.

The variation in time elapsed between the tonsillectomy and the reported examinations for the operated children is much greater than would appear from the age classifications in the table. At least 53 per cent of those operated on by seven years of age were known to have had the tonsils removed by six years of age, which would be six or more years prior to the date of the last physical check-up by the pediatrician. Among those tonsillectomized at eight years or older, the operation was at most four years and in many cases less than a year before the last of the reported health ratings.

Again, when the ages at which tonsils were removed were known to differ by as much as five years (early childhood versus late childhood) the trend of the findings remained the same. Detailed inspection of the records showed as many of the children tonsillectomized at five years or younger as of those at ten or eleven years of age were in relatively poor condition at the final examination in late childhood.

These comparative results indicate that at twelve or thirteen years of age, the great majority of the children whose tonsils had been removed were in good general condition, whether the tonsillectomy had been recent or some six or more years earlier.

Health status at maturity was determined from ratings given by the different examiners and the type of recommendations made at the final health check-up. All examinations were made in the summer months. The effect of tonsillectomy on general health has been studied by comparing individuals whose tonsils were removed before maturity with a control whose tonsils remained intact. The control group included: (1) those having tonsils free from clinical symptoms of infection—throughout childhood and at maturity; (2) those considered borderline cases, for whom indications for operation were not positive but whose tonsillar condition and history during the years of childhood suggested the need for surgical treatment; and (3) those definitely and repeatedly advised to have tonsils removed.

Comparative results are given in Tables II and III. On the whole, the trend of the findings is suggestive of better health of tonsillectomized individuals than of the nontonsillectomized, but the differences are not large. The rank of the groups according to the physician's ratings was respectively: first, those having tonsils out; second, those called borderline cases; third, those having "healthy tonsils"; and, last, those advised to have tonsils removed.

TABLE II

HEALTH RATINGS AT MATURITY OF TONSILLECTOMIZED AND NONTONSILLECTOMIZED CHILDREN

RATINGS	TONSILS OUT				TONSILS IN					
					HEALTHY TONSILS					
	BY 7 YEARS N = 54 PER CENT	8 TO 12 YEARS N = 46 PER CENT	13 TO 20 YEARS N = 22 PER CENT	SAMPLE GROUP N = 53 PER CENT	AT MATURITY N = 46 PER CENT	CHILDHOOD AND MATURITY N = 27 PER CENT	CHILDHOOD 8 TO 12 YEARS N = 49 PER CENT	T AND A QUESTIONED 8 TO 12 YEARS N = 44 PER CENT	T AND A ADVISED 8 TO 12 YEARS N = 24 PER CENT	T AND A ADVISED SAMPLE GROUP N = 30 PER CENT
General condition										
Very good	31	13	9	6	9	7	4	7	0	4
Good	50	70	63	53	58	56	63	63	54	23
Fair	19	13	23	28	26	37	31	25	33	60
Poor	0	4	5	13	7	0	2	5	13	13
Condition of nose, throat, ears, and eyes										
Very good	32	20	27	22	13	22	12	0	0	0
Good	59	67	55	42	52	52	39	29	25	7
Fair	9	13	18	34	33	26	49	66	75	47
Poor	0	0	0	2	2	0	0	5	0	46
Condition of teeth										
Excellent	59	39	41	31	35	29	33	18	29	37
Good	28	37	41	40	28	30	28	57	21	30
Fair	4	17	9	17	20	19	23	7	29	23
Poor	9	7	9	12	17	22	16	18	21	10

TABLE III

SOME SPECIFIC HEALTH PROBLEMS AT MATURITY OF TONSILLECTOMIZED AND NONTONSILLECTOMIZED CHILDREN

RECOMMENDATIONS ON IMMEDIATE HEALTH NEEDS	TONSILS OUT			TONSILS IN			
				HEALTHY TONSILS		T AND A QUESTIONED	T AND A ADVISED
	BY 7 YEARS N = 54 PER CENT	8 TO 12 YEARS N = 46 PER CENT	13 TO 20 YEARS N = 22 PER CENT	CHILDHOOD AND MATURITY N = 27 PER CENT	CHILDHOOD 8 TO 12 YEARS N = 49 PER CENT	8 TO 12 YEARS N = 44 PER CENT	8 TO 12 YEARS N = 24 PER CENT
Special medical care	50	57	50	52	73	82	92
Throat and tonsils	2	2	0	0	45	66	71
Sinus	13	17	18	4	14	21	25
Submucous resection	9	7	0	4	6	9	4
Ears	4	0	9	0	0	0	4
Eyes	41	41	36	41	49	32	46
General medical care	17	26	18	26	23	16	38
Dental care	52	54	55	70	71	71	83
Two or less caries	67	57	64	37	43	43	38
Eight or more caries	6	11	14	26	25	25	29
No recommendations for medical or dental care	30	17	27	15	8	5	0

The most outstanding finding in these results is that more than half of the boys and girls who had tonsils in and whose records from the age of eight to twelve years show positive indications for tonsillectomy, at maturity were in good general physical condition, in the judgment of the examiners. Frequency of reports of poor conditions were no higher among these cases with a history of diseased tonsils than among a sample of the population of the same age whose tonsils had been removed. However, certain specific signs of an unsatisfactory condition were more prevalent among the diseased tonsil group than among any other group studied.

The most consistent differences between the compared groups were noted in the frequency of recommendations for treatment of throat trouble (usually tonsillectomy) and for dental work. In five cases the tonsils had been incompletely removed and two of these were advised to have further surgical care. Among the control cases, 55 per cent were advised at maturity to have tonsils removed. In the sample of the population, 59 per cent of those whose tonsils remained intact were recommended to have them out.

Approximately half of the cases whose tonsils appeared to be healthy in childhood were advised at maturity to have them removed (45 per cent) and the majority of those formerly considered borderline cases now showed positive indications for tonsillectomy (66 per cent). On the other hand, a number of the children for whom definite clinical symptoms of diseased tonsils were continually reported during the early years of the study and who were frequently advised to have surgical treatment, when they grew up were found to have apparently healthy tonsils. While the group under observation was small, it is rather challenging to find that 28 per cent of the children who were repeatedly advised to have tonsils removed and who failed to follow the pediatrician's recommendation were at maturity no longer judged to need this operation, according to a throat specialist, and most of them were found to be in good all-round condition. Only one of the above cases was reported to be in poor condition.

It should be recalled here that the pediatrician's recommendations were never based on hurried decisions. He frequently saw the child a number of times before he finally advised surgical treatment. In the face of positive indications in childhood, the absence of infection in maturity certainly merits consideration.

In the Rochester, N. Y. study Kaiser reports, "The removal of infected tonsils and adenoids improves the chances of escaping dental caries, or, if it already exists, in improving the hygiene of the teeth and keeping the infection under control."[2] Our results tend to corroborate his conclusion in that healthy mouths were more frequent and the incidence of caries lower among the tonsillectomized group than among the control group.

After a careful examination the dentist recorded the number of cavities and pits in the enamel and other mouth conditions before he made a general judgment on the condition of the oral cavity. In the detailed findings and the recommendations as well as in the summary ratings, less evidence of dental infection was found among those whose tonsils were removed than among those having tonsils, regardless of whether the tonsils were or were not said to be infected. One out of three whose tonsils had been removed was free from dental caries at maturity while only one out of five among the control had this record. On the average, tonsillectomized cases had two carious teeth and the nontonsillectomized had four. The proportion in each classification having few and many caries is given in Table III.

Although dental cavities were more frequent among the group with tonsils than among those having tonsils out, this result cannot be considered as evidence of the association of infected tonsils with dental decay. Dental infection was reported just as frequently among young people whose tonsils were said to be free from clinical symptoms of disease as among those whose tonsils were said to be infected. The only inference warranted from these comparative findings is that young people whose throats were known to be "clean" by complete removal of the tonsils were more likely to escape dental infection than those having tonsils.

Sinus trouble, nasal obstructions, and ear trouble were reported as frequently in the tonsillectomized as in the control group. Incidence of these difficulties was lowest among cases having healthy tonsils throughout the investigation and highest among nonoperated children who were repeatedly advised to have the tonsils removed. For example, sinus trouble was reported three times less frequently among young people with a record of healthy tonsils than among those whose tonsils were removed in early childhood, and six times less frequently than among those for whom tonsillectomy had been recommended but not performed. Recommendations for treatment of sinus trouble in the order of occurrence were: 22 per cent of nonoperated cases, excluding those whose tonsils were considered healthy, 16 per cent of operated cases, and 4 per cent of those having healthy tonsils. Only two of the healthy tonsil cases were advised at maturity to have treatment for either sinus, nose, ear, or throat trouble. Incidence of one or more of these recommendations is shown in Table IV.

Need for general medical care was as prevalent among the tonsillectomized as among the control cases. Although a slightly larger proportion of those previously advised to have their tonsils removed than of any other group studied were now recommended to consult a physician, the differences were neither large nor consistently in favor of those having tonsils out or in. Young people whose tonsils were con-

TABLE IV

	TONSILS OUT			TONSILS IN			
	CHILDHOOD		ADOLESCENCE	HEALTHY IN CHILDHOOD AND MATURITY	HEALTHY IN CHILDHOOD	T AND A	
	EARLY	LATE				QUESTIONED	ADVISED
						IN CHILDHOOD	
Treatment for: Ears, nose, or throat	22%	26%	27%	7%	49%	73%	92%

sidered in childhood as borderline or questionable cases were least often in need of general medical care. Those having tonsils were no more frequently referred for medical service than those having tonsils out.

However, in general, the tonsillectomized cases were more frequently given a clean bill of health by the examiners than the control cases. The findings show that among the tonsillectomized group, one out of four was in need of neither medical nor dental service at maturity, while among the nontonsillectomized group the proportion was one out of twenty. Every individual who during the childhood years had been advised to have his tonsils out but did not was in need of some health service, i.e., either medical or dental care.

The significant point to these results is that so many ostensibly well young people are in need of medical care. At least one out of every five who were examined periodically over a twelve-year period was advised to consult a general physician at maturity and three out of four required some type of medical service. On the whole, there was little evidence of a general relation between the presence or absence of tonsils and the need for this medical care.

A brief summary is given in Table III of the type of recommendations made, i.e., special medical care, general medical care, and dental care. Such care was required by 75 per cent of the tonsillectomized cases, 85 per cent of those whose tonsils were considered free from infection, and 95 per cent of those for whom clinical symptoms of infected tonsils had been reported during the childhood years.

SUMMARY AND CONCLUSIONS

In connection with a health education program conducted by the Elizabeth McCormick Memorial Fund in cooperation with the public schools of Joliet, Ill., a group of 415 so-called "well" children were given annually a thorough physical examination from the age of eight or nine years to twelve or thirteen years by a pediatrician. At the age of twenty or twenty-one years, 238 of them were reexamined by physicians and a dentist. One hundred six other young people living in the community, who were of the same age and from a similar socioeconomic level but who had had no direct contact with the former program, were examined by the same corps of specialists. Results of a careful analysis

of the health records of these 521 individuals with respect to the influence of tonsillectomy on their general health is here reported.

Comparative findings are presented on the health status of 175 boys and girls whose tonsils were removed and a control group of 166 whose tonsils were intact at maturity. The control group included 68 individuals whose tonsils were said to be free from clinical signs of infection and 98 for whom tonsillectomy had been questioned or advised. Results are in agreement with those of other investigators in showing that beneficial effects do not always follow the removal of tonsils.

In the present study removal of tonsils did not appear to prevent the development of various ailments and physical defects. When compared with a control group who were never advised to have the tonsils out, the tonsillectomized children were in a less satisfactory physical condition at maturity in many respects than the control group. However, on the whole, a larger proportion of the tonsillectomized children were judged to be in good general health and fewer of them were in need of remedial work, both during late childhood and at maturity, than of the nonoperated children, although the differences were not always large.

Age at which tonsils were removed appeared to have little influence on general health status during the years covered by this investigation. Children tonsillectomized during early childhood were in need of as extensive medical care at maturity and for the same types of conditions as those operated on during late childhood or adolescence.

Among the cases followed from childhood, the nonoperated children who had been definitely and repeatedly advised to have the tonsils out, as a group, were in poorer condition at maturity than those who had the operation. Individually, there were outstanding exceptions. The later records of one out of every six cases in which indications for tonsillectomy had been positive during childhood showed not only a satisfactory throat condition, according to a throat specialist, but a good general health status.

Comparisons of the nonoperated children who were advised to have tonsils removed with a sample group of the adolescent population who had had the operation indicated that the nonoperated were in as good all-round condition at maturity and were in need of no more remedial care than those whose tonsils had been removed.

Results of this long-term investigation give no conclusive evidence of outstanding differences in general health status between young people whose tonsils were removed in childhood and that of those who were advised to have the operation but did not follow the physician's recommendation.

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THE NORMAL ADDIS SEDIMENT COUNT IN CHILDREN

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COMPARATIVELY few quantitative studies have been made of the normal urinary sediment, particularly in children. Addis[1] in 1926 suggested this method of study and proposed normal standards. These standards were based upon a study of 74 healthy young adults and have been generally accepted by those using the Addis technique in urinary examination in adults. In 1933 Lyttle[2] published a study of the Addis count in normal children. His study included 74 children; the results were in close agreement with Addis' findings, although a slightly higher excretion of casts and protein was noted.

The present study was undertaken for two reasons. First, to establish the normal variations of the Addis count in children; and second, to demonstrate if possible the presence of unsuspected and undetected latent glomerular nephritis in a group of presumably normal children. This study includes urinary sediment counts upon 202 children seen in the Stanford out-patient children's clinic and the Stanford Convalescent Home between January and July, 1936. No effort was made to select the children studied except for the exclusion of children having had any recent infection, those giving a history of previous glomerular nephritis, and those presenting any evidence or history of rheumatic infection. Children showing values of the Addis count higher than the previously published normal standards of Addis were checked carefully to prevent the inclusion of ill or abnormal children in this group. It is felt that the children studied represent as nearly as possible normal children seen in clinic practice.

The usual procedure for the Addis concentration test was carried out, with the restriction of fluids on the day preceding the test, and the collection of a timed, concentrated specimen. The casts, red blood cells, and white and epithelial cells were counted in a counting chamber, and an estimation of the protein was done by the method of Shevky and Stafford, as slightly modified by MacKay (Peters and Van Slyke[3]). All values were computed upon theoretical twelve-hour volumes.

The number of casts excreted in twelve hours was found to range from 0 to 29,000. One hundred twenty-eight children had no casts. The mean value was 1,230 with a standard deviation of 3,900. The range up to 9,000 casts would include about 95 per cent of all normal values.

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This is an increase over the Addis standard of 5,000 and approximates Lyttle's findings. All the casts noted were hyaline and granular.

Red blood cells were found to vary from 0 to 800,000. One hundred and eleven children had no red blood cells. The mean value was 81,600 with a standard deviation of 116,300. This is a slightly higher value than that found by either Addis or Lyttle. In clinical practice we have come to regard with suspicion any red blood cell count of 600,000 or more, and statistically a red cell count above 314,000 is significant.

The striking difference between the present findings and those of Addis and of Lyttle is the twelve-hour protein value. In this series the protein excretion ranges from 5 to 90 mg. with a mean of 28.5 mg. and a standard deviation of 13.2. Inasmuch as the mean plus two times the standard deviation of 13.2 includes approximately 95 per cent

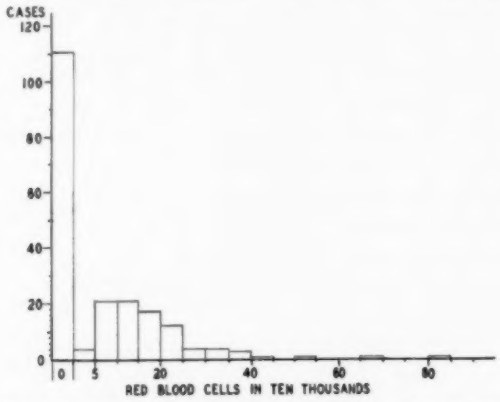

Chart 1.—Number of red blood cells in twelve hours (201 sediment counts).

of the values found, a protein excretion over 55 mg. would be statistically significant. This is a definite increase over the upper limit of 30 mg. of Addis and 35 mg. of Lyttle. As 10 to 15 mg. per cent will give a faint cloud by the heat and acetic acid test, such a concentration can easily be conceived to occur in moderately concentrated, normal urine. This is the probable explanation for the faint cloud of protein that is so frequently reported in analyses of children's urine.

White and epithelial cells were not counted in this series. Many of the subjects were girls and the collection of catheterized specimens was not practicable in the out-patient department. While careful cleansing prior to voiding usually prevents contamination in such cases, the results were not dependable enough for analysis. However, my impression has been that the normals of Addis and Lyttle are satisfactory.

Of the 202 children studied, one was found to have definite glomerular nephritis. Her history is as follows:

J. B., one of twins, was born Oct. 10, 1927. Secondary anemia and gastric anacidity were found in May, 1929. She had frequent upper respiratory infections during the next few years. Bilateral mastoidectomy was done in May, 1929. A Vincent's angina occurred June, 1930. Residual microcytic anemia was found in 1935, and in November, 1935, she was sent to the Stanford Convalescent Home with

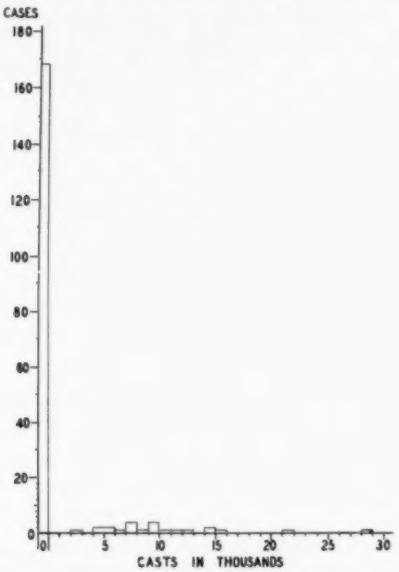

Chart 2.—Number of casts in twelve hours (201 sediment counts).

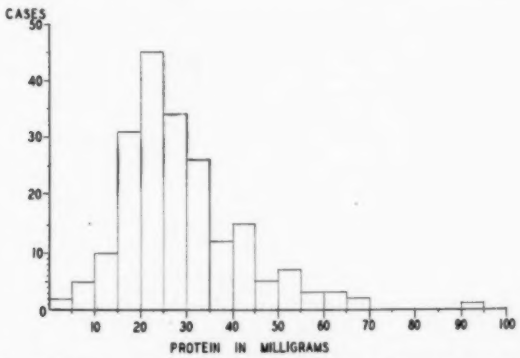

Chart 3.—Milligrams of protein in twelve hours (201 sediment counts).

a diagnosis of malnutrition and secondary anemia. Frequent urinalyses were done over the period of observation, and, with the exception of the slightest possible trace of protein reported in June, 1930, all examinations were negative. There was never any history of hematuria or edema. She grew and developed fairly normally but was always smaller than her twin sister, and she was noticeably malnourished when she was sent to the convalescent home. Physical examination revealed nothing

TABLE I

COMPARISON OF STANDARDS

	ADDIS			LYTTLE			PRESENT STUDY			PROPOSED UPPER LIMITS
	AVERAGE	LOWEST	HIGHEST	AVERAGE	LOWEST	HIGHEST	AVERAGE	LOWEST	HIGHEST	
Casts	1,040	0	4,270	1,085	0	12,916	1,230	0	29,000	10,000
Red blood cells	65,750	0	425,000	15,181	0	129,000	81,600	0	800,000	600,000
White and epithelial cells	322,500	32,400	1,835,000	322,184	9,000	2,822,000	/	/	/	2,000,000
Protein				18.5	3	47	28.5	5	90	55 mg.

except the malnutrition and chronic tonsillitis. Blood pressure was within normal limits. There was never any evidence of purpura or scurvy. The sediment counts listed in Table II were done after the first routine Addis count revealed an abnormal increase in red blood cells in the urine.

TABLE II

DATE	CASTS (12 HR.)	TYPE OF CASTS	RED BLOOD CELLS (12 HR.)	WHITE AND EPITHELIAL CELLS (12 HR.)	PROTEIN (MG.)	VOLUME	SPECIFIC GRAVITY
1/16/36	0		846,000	940,000	24	188	1.025
2/13/36	0		1,420,000	284,000	20	142	1.028
2/20/36	0		1,950,000	151,000	20	151	1.029
2/27/36	2,000	Blood casts present	1,514,000	0	24	169	1.028
4/ 4/36	12,000	100% hyaline	756,000	216,000	56	216	1.028
6/17/36	0		510,000	170,000	18	170	1.028
3/17/37	0		2,000,000	1,000,000	44	152	1.028

The detection of latent glomerular nephritis in J. B. is of theoretical interest. There can be no doubt that latent glomerular nephritis does exist in individuals who are completely unaware of any renal lesion. It is common experience for patients to come to the physician complaining of edema, headaches, visual disturbances, or other symptoms of degenerative or terminal glomerular nephritis, and giving no history of the initial stage. It is obvious that such patients must have had a latent glomerular nephritis for years, during which time the kidneys were slowly progressing toward renal insufficiency, but with no symptoms. The demonstration of Addis that glomerular nephritis may continue in a latent stage for years after a clinically apparent initial stage is now generally accepted. Finally Snoke[4] described 14 cases of latent glomerular nephritis in children, all discovered accidentally, and none presenting a story of the initial stage.

The explanation for this unrecognized renal lesion is probably the subclinical initial stage of glomerular nephritis. Observations of Addis,[5] Lyttle,[6] and Snoke[4] have demonstrated actual glomerular nephritis following streptococcal infections in which there were no symptoms of edema, or gross hematuria. In these cases unless specific search for the renal lesion had been made by the concentration method, the glomerular nephritis might well have been missed.

The finding of one case of latent glomerular nephritis in 202 presumably normal children is of course statistically insignificant. But the existence of such cases in the general population is significant, and the fact that special technique of urinalysis is required to determine the existence or extent of the renal lesion is important.

The use of the Addis technique in routine urinalysis is perhaps impractical, but its employment in all cases in which the slightest urinary abnormality exists or in life insurance examinations is well worth consideration.

CONCLUSIONS

1. Quantitative study by the method of Addis was done upon the urinary sediment of 202 presumably normal children.

2. The numbers of casts and red blood cells excreted in twelve hours were found to be in close agreement with those reported by Addis and Lyttle.

3. The protein excreted in twelve hours was found to vary from 5 to 90 mg. with a mean of 28.5 and a standard deviation of 13.2, a definite increase above the amount reported by others as normal. The upper limit of normal protein excretion should be raised to 55 mg.

4. One case of previously unsuspected and unrecognized latent glomerular nephritis was discovered in the routine urinalysis by the Addis-technique of 202 presumably normal children.

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TUBERCULIN REACTIONS IN CHILDREN

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DURING the past thirty years since the development of the tuberculin test by von Pirquet many variations of this test have been devised and countless studies published. The relationship of the intensity of the tuberculin reaction to the type of disease or activity of the lesion has been a favorite subject. Years of intensive study on the part of many clinicians have apparently led only to contradictory reports. We, also, were tempted by the possibility of finding valuable correlations, but after many trials we had to agree with previous investigators that no definite proof can be advanced that the size and intensity of the tuberculin reaction is of any help either in localizing the lesion or making the prognosis more accurate. It is not our purpose, therefore, to add to the existing mountain of statistics. But in studying our material we frequently encountered practical problems related to the use of tuberculin in testing for which we could find no solutions in the literature, and we have therefore tried to answer certain questions regarding the technique of administering the tests, care of syringes and solutions, reading of the tests, intervals between tests, and use of various controls.

The material for our study came from three main sources in Bellevue Hospital, from the wards of the Children's Medical Service, and from two out-patient clinics, (1) the chest clinic of the Children's Medical Service and (2) the children's clinic of the Tuberculosis Service. In all these groups a tuberculin test is part of the routine examination of all patients. The ward service consists of acute and chronic cases from birth to twelve years with a well-baby or boarding ward included. Only a very small percentage of the admissions are for tuberculosis. Moreover, many of the children suffer from minor defects or illnesses such as scabies which prevent their admission to boarding or detention homes but which would not ordinarily lead to hospital care. In the chest clinic we see patients with all types of chest disease in consultation with the other services and from our own out-patient department, as well as children who have been in contact with adults from the Tuberculosis Service. The children's clinic of the tuberculosis service, under the Department of Hospitals, is a clinic which cares for the children of the known tuberculous individuals residing in the Bellevue Hospital district. Tuberculin tests are given all new patients admitted and yearly thereafter in all negative cases, of which there are quite a number. Our material

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therefore does not comprise a group of sick children but is rather a cross-section of children of the Bellevue Hospital district. Moreover, while many of the children in the ward group are known only through their hospital stay, the children from both out-patient department groups have often been studied over a long period of years.

For the main part of this study we have used only cases for which the following information was available: the birth date and sex of the child; the dilution and amount of the tuberculin solution used for testing; and the size of the reaction expressed in millimeters. We have used only cases in which a roentgenogram of the chest taken approximately at the time of the tuberculin test was available for reading by E. M. L. or A. R. In addition, we know in all cases the diagnosis or reasons why the children were in the hospital or clinic. Moreover, in most cases the nationality, color, height, and weight of each child were recorded, and a note was made of possible exposure to tuberculosis, giving relationship of the child to the infecting case and the duration of exposure wherever possible. The study covers the years 1930-1936.

TECHNIQUE

All tests were done with New York City Board of Health Old Tuberculin (O.T.) which is supplied in a special outfit originally suggested by Charles Hendee Smith. A capillary tube of tuberculin is supplied with a 10 c.c. vial of sterile normal saline solution; when mixed this gives a solution of tuberculin 1:1,000. Of this solution, 0.1 c.c. equals approximately 0.1 mg. of tuberculin. To obtain the higher dilution, 1 c.c. of this standard solution was added to 9 c.c. of normal saline, making a solution of tuberculin 1:10,000, so that 0.1 c.c. of the resulting solution equals approximately 0.01 mg. of tuberculin; and for the more concentrated dosage the capillary tube containing the tuberculin was mixed with 1 c.c. of saline instead of 10 c.c. making a solution of tuberculin 1:100 so that 0.1 c.c. of the resulting solution equals approximately 1 mg. of tuberculin. No solution was used more than one week, and usually fresh solutions were made twice weekly. All solutions not in use were kept in the refrigerator.

The question of the stability of dilutions of O.T. has been a subject of much debate. For many years inquiries were made of individuals well acquainted with tuberculin and its uses, and, since no satisfactory answers were obtained, in 1933 we labeled and set aside dilutions of O.T. in strengths 1:1,000 and 1:10,000. Duplicate vials were stored in a desk drawer and in the refrigerator. Eighteen months later similar solutions were put aside. The solution kept out of the refrigerator for two years developed a flocculent white precipitate and was consequently cultured (with negative results) before using. The solutions were then used for testing children in the regular way, freshly diluted tuberculin being used in the same strength as controls. Care, of course, was taken

not to test children with tuberculosis in whom the double dosage of the lower dilution might do harm. Of the 40 cases tested with 0.1 c.c. of tuberculin solution in 1:10,000 concentration kept out of the refrigerator six months and with equal amount of freshly mixed O.T. solution in the same concentration, 21 reacted negatively to both, and 19 positively to both solutions. Moreover, the positive reactions were of approximately the same size and intensity in both series. Of 11 cases which reacted to a fresh solution of O.T. in dilution of 1:10,000, only 8 reacted to the same dose of the dilution made two years previously.

Since 70 per cent of the children reacted to the two-year-old dilution and since 100 per cent reacted to the six-month-old dilution kept out of the refrigerator, it seems safe to declare that dilutions of tuberculin up to 1:10,000 need not be made oftener than once a month and that they need not be kept constantly in the refrigerator if handled with ordinary care. This should prove a considerable saving of time and money in clinics and hospitals where much tuberculin testing is done.

Separate syringes and needles were kept for the different dilutions and were not used for any purpose other than Mantoux testing. Since tuberculin is thermostable, boiling alone does not remove the factor to which the skin reacts, and as Charles Hendee Smith[1] and others have pointed out, tuberculin syringes should not be used for controls or other tests. In order to find out if possible by what means a syringe once used for tuberculin can be rendered tuberculin free, some brief experiments were undertaken.

A group of 20 children who reacted to a Mantoux test in a dilution of 1:10,000 was used for further testing. A new tuberculin syringe and needles were filled with a fresh solution of O.T. in dilution of 1:10,000. After the expulsion of the solution the syringe and needles were boiled five minutes, then filled with normal salt solution, and 0.1 c.c. injected intracutaneously into each of the 20 children. Fourteen of the 20 showed redness and induration varying from 5 by 5 mm. to 10 by 10 mm. at twenty-four hours, and 8 of the 20 showed redness and induration in no case larger than 14 by 20 mm. at forty-eight hours. In 40 per cent of the cases, therefore, the control test with normal saline after boiling of the syringe gave tests which might have been interpreted as positive tuberculin tests, although in most cases the reaction was smaller in size than the previous tuberculin test.

A second experiment was carried out at the same time on all 20 children. Another new syringe and other needles were filled with tuberculin in dilution of 1:10,000. The syringe and needles were then rinsed ten times with 95 per cent alcohol, and three times with normal saline, after which 0.1 c.c. of normal saline was injected subcutaneously into each of the children. At twenty-four hours, 6 of the 20 children had redness and induration varying from 5 by 5 mm. to 10 by 10 mm. at the site of the injection, and at forty-eight hours, five still had the same

signs so that approximately 30 per cent had a reaction to saline solution which could have been interpreted as a positive tuberculin reaction, although again the reactions were small in all the cases.

Therefore, the contention that neither boiling nor rinsing of a syringe previously used for tuberculin is enough to remove all traces of even a high dilution of O.T. is shown to be true, and the technique of keeping separate syringes and needles for tuberculin testing is justified. Moreover, it would seem advisable to keep separate syringes for each dilution.

As to the possibility of creating a false positive tuberculin reaction by repeated injections of tuberculin in the skin of an unsensitized individual, we agree with Hamman and Wollman[2] that "single or repeated injections of large or small amounts of tuberculin in healthy animals never occasion tuberculin hypersensitiveness." In 1931 we did repeated injections of tuberculin from 0.05 mg. to 1.0 mg. at two-to-five-day intervals in seven children ranging in age from two months to twelve years, all of whom had had negative tuberculin tests within a month. The area into which the tuberculin was injected was carefully marked with ink so that the subsequent injections were made at precisely the same site. Each child received from four to seven injections. The results were completely negative. No staining or pigmentation of the skin was observed in any case, and subsequent roentgenograms of the chest were negative on all cases.

We believe with many others that the standard method for group tuberculin testing should be a complete intracutaneous test beginning with a dose of 0.1 c.c. of a 1:10,000 solution, then 0.1 c.c. of a 1:1,000 solution and ending with 0.1 c.c. of a 1:100 solution. In special cases it may, of course, be desirable to begin with a much higher dilution or to carry the testing on with more concentrated solution. We used the scheme of dosage and the dilutions given because the amount of fluid injected is the same in all doses, eliminating any possible objections to interpretations of the size of the reaction, and because of the variations in the amount of solution injected. The amounts are easily measured and mistakes in dosage unlikely to occur. Since the same scheme has been used in many other series reported, our results are comparable. The only disadvantage of starting with 0.01 mg. is that invariably some children will fail to return for the next dose. However, the disadvantages of beginning with 0.1 mg. would seem to outweigh this fact since the local reaction may be severe, general reaction may occur, and we have had several instances in which a focal reaction has occurred.

READING OF TUBERCULIN REACTIONS

All tests were measured with a millimeter rule by one of the writers or by a specially trained assistant and were graded according to the scheme of Hetherington McPhedran and associates.[3] An induration of 10 mm. in diameter or less constituted a one-plus reaction; from 10 to

15 mm. two-plus; more than 15 mm. three-plus; and a reaction with necrosis in addition to induration or one associated with general reaction, four-plus.

It is impossible to make a diagnosis of a tuberculin test after twenty-four hours. There may be essentially nothing to see at the site of injection, and yet the test may be definitely positive at forty-eight hours and subsequently. The height of the reaction is usually reached at forty-eight hours but it must be emphasized again that no test should be considered positive, which does not last more than forty-eight hours because every positive test is still definite at seventy-two hours although it may have already decreased slightly in size and intensity. False positive reactions, on the other hand, which usually show only marked redness but may occasionally show slight induration, usually reach their height very early and are definitely fading at forty-eight hours. Induration is a greater criterion of the positive test than redness. It should measure at least 5 mm. to constitute a positive reaction. A delayed reaction to a tuberculin test is uncommon but may occur. A test completely negative at forty-eight hours may first show redness and induration at seventy-two hours (or rarely, even at ninety-six hours) and go on to pigmentation. Therefore the ideal times for reading tests would be forty-eight hours and five days, and for rapid testing the next dilution could be given when the previous test is negative after five days. This is a good scheme on wards but in dispensary practice weekly intervals for final readings and retesting are more practical. A single reading is undesirable but if unavoidable had best be done at seventy-two hours.

In clinics where large numbers of tuberculin reactions are constantly being read, few doubtful reactions are seen, and the false positive reactions are usually easily recognized. Reference is not made here to false reactions resulting either from trauma or secondary infections, which are usually obvious, but to those reactions in which erythema of considerable size is the main feature of the response to the injection of tuberculin and where induration, when it occurs, is slight and ill defined. If the tester is not very experienced, the practice of running up the dosage in doubtful cases often clarifies the results, as a weak positive will give a more definite positive with a stronger dilution. In cases where all three doses give the same equivocal reaction, two other preparations are available to decide the nature of the reaction.

Purified protein derivative, or P.P.D. as it is usually called, has been developed by a special committee of the National Tuberculosis Association as a substitute for O.T. Individuals reacting to O.T. are said invariably to react to P.P.D., and, since it is free from any of the impurities inherent in O.T., it may be used as a possible final criterion in doubtful cases. In some cases atypical reactions are undoubtedly due to the protein of the broth in which the tubercle bacilli were grown, so

that plain broth may also be used as a control. We have not used saline solution as a control because it seems to be generally recognized that it is of little or no value.

We selected 26 cases with negative chest roentgenograms and no evidence of tuberculosis but with similar indefinite reactions to all dilutions of O.T. up to 1 mg. The reactions included for study were variable, ranging from an area of erythema of 7 mm. to one as extensive as 45 by 75 mm. The erythema was usually evenly diffuse but at times presented a mottled appearance. In one case which on further testing proved to be negative, slight pigmentation persisted for one week after injections. In 9 cases a slight but definite induration accompanied the erythema. Each child received at the same time 0.1 c.c. of a 1:100 solution of broth intracutaneously on the left arm and 0.1 c.c. of 0.05 mg. P.P.D. (corresponding to 1 mg. O.T.) on the right arm. Twenty-one of the 26 children had no reaction to P.P.D., and 10 gave a positive reaction to broth. One child had a definitely positive P.P.D. reaction (20 by 22 mm. in size) and a negative broth reaction. Therefore in 22 out of the 26 children, or 84.6 per cent, P.P.D. gave the final decision with only one child positive to P.P.D. who had reacted equivocally to O.T. Of the remaining 4 cases, 3 gave exactly similar reactions to P.P.D. and O.T., and all 3 had negative broth reactions; in the one remaining case, there was an erythema reaction of approximately the same size to O.T., P.P.D., and broth. In these last 4 cases, representing 15.4 per cent of the group, it was impossible to decide the cause of the erythema, but it was undoubtedly not a positive tuberculin reaction. It is obvious that P.P.D. can be of great value as a control in deciding most doubtful cases and may largely replace the use of broth. It may be that P.P.D. will ultimately replace O.T. for testing, but we are concerned in this report only with its use as a possible final criterion in doubtful cases. One obstacle to its general use is the fact that solutions of P.P.D. are apparently not stable and the dilutions must be freshly made.

There were 1,264 cases with carefully measured tuberculin reactions available for complete analysis, and, as stated before, all attempts to correlate the size and intensity of the tests to factors such as site of the tuberculous disease, activity of the lesion, or prognosis were completely unsuccessful. There were only two factors which varied directly with the size and intensity of the tuberculin reactions, the amount of tuberculin injected, that is, the strength of the dilution, and the age of the individual tested.

There is a definite relationship between the amount of tuberculin injected intracutaneously and the size and intensity of the reaction. In 404 cases in which 0.01 mg. and 0.1 mg. were given simultaneously,* the reaction to the larger dose was greater in 289, or 71.5 per cent of cases,

*This was originally instituted because of the limited stay of most ward patients so that we could measure the reactions to the smaller dose but not miss the patient who would only react to a larger dose.

and approximately equal in the remaining cases. In no case was the reaction to 0.01 mg. larger than to 0.1 mg. Moreover, as shown in Table I, in 738 readings of positive tuberculin tests with 0.01 mg. only 17, or 2.3 per cent, had a four-plus reaction, whereas of 526 cases tested with 0.1 mg. (or in some cases with 0.05 mg.) 40, or 7.6 per cent, showed this severe reaction.

TABLE I

RELATION OF SIZE OF DOSE TO REACTION AT ALL AGES

NO. OF CASES	AMOUNT OF TBN. INJECTED	INTENSITY OF REACTION			
		% +	% + +	% + + +	% + + + +
738	0.01 mg.	23.3	30.4	43.9	2.3
526	0.1*	8.2	25.0	59.2	7.6

*In some cases 0.05 mg. was used on the wards instead of 0.1 mg. The measurements of the tests so closely approximated those with 0.1 mg. that we feel justified in including these tests as if they had been done with 0.1 mg.

The tendency for the tuberculin reaction to become more marked as the child grows older is shown definitely with the 1:10,000 dilution, and even more strikingly with the stronger dilutions.

Tables II and III show that it is much safer to begin testing with 0.01 mg. than with 0.1 mg. as the risk of severe reactions is much diminished by starting with the smaller dose. It may be justifiable occasionally for practical reasons to begin the testing of infants with 0.1 mg. since the reactions tend to be small at this age, but it is a safe rule to give an initial dose of 0.01 mg. after the age of four years.

TABLE II

RELATION OF INTENSITY OF REACTION TO AGE

AMOUNT OF TBN. 0.01 MG.		INTENSITY OF REACTION			
AGE (YR.)	NO. OF CASES	% +	% + +	% + + +	% + + + +
Under 5	205	29.7	36.5	32.2	1.6
5-10	356	23.0	27.7	46.1	3.0
Over 10	177	16.3	28.8	53.1	1.7

TABLE III

RELATION OF INTENSITY OF REACTION TO AGE

AMOUNT OF TBN. 0.1 MG.		INTENSITY OF REACTION			
AGE (YR.)	NO. OF CASES	% +	% + +	% + + +	% + + + +
Under 5	141	12.0	37.5	42.5	7.8
5-10	283	7.4	22.2	62.1	8.1
Over 10	102	5.8	12.7	75.3	5.8

It is important that every effort be made to run up the dosage in cases negative to 0.01 mg. or a relatively large number of positive tests will be overlooked. Of 182 ambulant and afebrile patients in the dispensary who were negative to 0.01 mg., 27, or 14.8 per cent, were positive to subsequent injections of 0.1 mg., and of the 155 children who were negative to both, 17, or 10.9 per cent, were found positive to 1 mg.;

thus in all, 44 cases, or 24.2 per cent of the total, were uncovered which would have been missed if only the small initial dose had been given. On the wards the difference was even more marked. Of 381 children, 25 per cent of those negative to 0.01 mg. were subsequently found positive to 0.1 mg. We believe that the difference in figures from the dispensary and ward groups is due to the fact that many children are admitted to the ward with high fever, a factor known to suppress tuberculin allergy. Since relatively few children remain on the ward long enough to receive the third test with 1 mg. when the two previous ones have been negative, we cannot quote figures on the percentage of children positive to 1 mg. on the wards with previous negative tests, although these do occur.

We were interested in trying to determine any sex variation in size of reactions, and analyzed our figures accordingly. As shown in Table IV, the figures for the two sexes are almost identical.

TABLE IV

SEX IN RELATION TO INTENSITY OF TBN. REACTION

AMOUNT OF TBN. 0.01 MG.	MALE		FEMALE	
INTENSITY OF REACTION	NO. OF CASES	%	NO. OF CASES	%
+	85	23.6	89	24.6
++	117	31.6	107	29.9
+++	165	42.8	159	43.3
++++	8	1.9	8	2.2

STABILITY OF POSITIVE TUBERCULIN REACTIONS

In an effort to discover how long a positive tuberculin test persists in childhood, 113 children with initial positive intracutaneous tests were subjected to repeated tests at varying intervals. Of these, 111 remained positive after intervals of five to twelve years, and 99 of these reacted to the initial dose, 0.01 mg. Only four children showed variations in allergy. For instance, an infant with a primary complex and a positive tuberculin test in 1926 with 0.1 mg. had a positive test with the same dose in 1929, then a negative test with 0.01 mg. in 1932, and a final positive test with 0.01 mg. in 1936. No cause was found for the variations in allergy, and it is possible that, if the dosage could have

TABLE V

STABILITY OF POSITIVE TBN. REACTIONS

INTERVAL AFTER INITIAL POSITIVE TEST (YR.)	NO. OF CASES RETESTED	NO. OF CASES WITH POSITIVE REACTIONS
5	58	57
6	25	24
7	11	11
8	10	10
9 to 12	9	9

been increased in these few cases, and the tests repeated, positive reactions to the stronger dilutions would have been obtained. In three cases a definitely decreasing allergy could be demonstrated. One child showed a positive test with 0.1 mg. and finally after five years a test negative with 0.1 mg. but positive with 1 mg. Another case was positive to 0.1 mg. in 1925, negative to 0.1 and positive to 1 mg. in 1930, negative to 1 mg. and positive to 2 mg. in 1933, and again in 1935. The third case, originally positive to 0.1, after six years required 2 mg. for a positive test. In only two cases did an original positive test become negative to 1 mg. after lapses of five and six years and remain so. Neither of these children would return to clinic so that tests could be made with more than 1 mg. The children who became negative to tuberculin after lapses of five and six years had no evidence of tuberculosis, aside from the initial positive tuberculin test.

TABLE VI

INCIDENCE OF POSITIVE TBN. REACTIONS

AGE	TOTAL NO. CASES TESTED		TOTAL NO. POSITIVE REACTORS		% OF POSITIVE REACTORS	
	1921-28	1930-36	1921-28	1930-36	1921-28	1930-36
0- 6 mo.	1425	1214	48	9	3.4	.7
6-12 mo.	982	1238	79	66	8.0	5.3
1- 2 yr.	1088	1578	136	159	12.5	10.0
2- 4 yr.	1106	1933	167	300	15.6	15.1
4- 6 yr.	817	1518	152	294	18.6	18.1
6- 8 yr.	794	1292	209	302	26.3	23.5
8-10 yr.	735	1273	211	342	28.7	26.9
10-12 yr.	638	1090	248	355	38.8	32.6

It would seem reasonable to assume from these figures that a positive tuberculin test, especially when a diagnosis of primary tuberculosis has been established, rarely tends to become negative during childhood. This would mean that a negative tuberculin test is of great significance in excluding tuberculosis in children, and we believe this to be true. In an extensive experience on the wards for the past fifteen years we have never seen a case of tuberculosis with a negative tuberculin test to 1 mg. unless the child had just recovered from measles or was in a moribund condition. In a recent study of 352 ambulant children in the dispensary with definite roentgen or clinical evidence of active or healed tuberculosis, we have seen only two with negative tuberculin tests and both had roentgenograms showing apparently well-calcified primary lesions. One child was negative to 1 mg. at nine years of age, negative to 10 mg. at twelve years of age; the other was negative to 1 mg. at five years and could not be returned for further testing. It is, of course, recognized that in later life the occurrence of cases with negative tuberculin tests and calcified primary foci is not rare. We merely wish to emphasize that the association of a negative tuberculin test with a healed lesion is apparently uncommon before twelve years of age. Most careful thought

should be given to a questionable lesion in a child with a negative tuberculin test before it is pronounced tuberculous. In both cases in which we made such diagnoses within the past fifteen years we were in error. One case was declared nontuberculous after operation, and in the second case with a supposed tuberculosis of the spine, autopsy showed actinomycosis.

If then a child with a positive tuberculin test is likely to remain positive during childhood, we can see no advantage in repeating the test since it gives no added information helpful in diagnosis or prognosis. Moreover, repetition of tuberculin tests may be definitely harmful. One child developed a phlyctenular conjunctivitis following a repetition of the tuberculin test. Another with a receding primary reaction showed within twenty-four hours an increase in the size of the perifocal reaction and a small pleural effusion. These are only two examples from many that we have seen. Granted that such occurrences may happen from auto-tuberculinization, why add the extra risk of a tuberculin test? We are not denying, but trying to emphasize, that tuberculin properly used may be of great assistance in selecting infected cases and in differential diagnosis, but we believe that the dangerous potentialities of tuberculin must not be overlooked.

Since 1918 there has been a steady decline in the death rate in New York City from all forms of tuberculosis. A great effort has also been made to hospitalize and segregate seriously ill patients and to remove children from contact with known tuberculous persons. In order to see if these factors had served to decrease the number of children infected with tuberculosis as shown by the tuberculin test, we assembled for comparison C. H. Smith's data from Bellevue Hospital wards[1] for the years 1921-28, and our figures from the same wards for the years 1930-1936.

The figures show a marked decrease in tuberculous infection in the first year of life with an appreciable decrease between the ages of one and two years, and again in the oldest age group. The percentage of cases of all ages found positive in 1921-28 was 17 per cent and in 1930-36 was 16.4 per cent. It would seem therefore that, whereas the total number of children twelve and under infected with tuberculosis has not decreased markedly in the past seven years as compared with the eight-year period studied by Smith, yet there has been a marked decline in infection in infancy, which we hope is a reflection of attempts at the speedy removal of infants from contact with cases of tuberculosis and which should encourage us to stress greatly this preventive measure.

SUMMARY

1. In a study of 1,264 measured tuberculin reactions, no positive correlations could be found between the size and intensity of the reactions and the location of tuberculous disease, the size or activity of the lesion, or the prognosis.

2. The reaction to the intracutaneous tuberculin test tends to vary in size and intensity directly with the size of the dose and with the age of the child.

3. There is no sex variation in the size and intensity of the reaction when age and dosage are constant.

4. The initial test should not be more than 0.01 mg. and a negative test should mean negative to 1 mg.

5. Definite criteria as to size of reaction and time of reading must be adhered to if false reactions are to be eliminated.

6. Tuberculin dilutions up to 1:10,000 are relatively stable, and dilutions need not be made more often than once a month.

7. Syringes and needles should be used for tuberculin testing only and separate ones kept for the various dilutions.

8. A positive tuberculin reaction is unlikely to become negative within the span of childhood, and this is even less likely to occur in cases in which there has been a diagnosis of clinical tuberculosis than in cases in which the positive test has been the only manifestation of tuberculosis.

9. It is usually unnecessary and undesirable to repeat a tuberculin test during childhood if a tuberculin test has once been positive, as the test only rarely becomes negative during these years.

10. There has been a marked decrease in the number of infants infected with tuberculosis in the series studied on the Children's Medical Service of Bellevue Hospital in the past seven years as compared with a similar preceding period.

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FOLLOW-UP REPORT OF 99 CHILDREN WHO RECEIVED FEVER THERAPY FOR CHOREA

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THIS paper is a brief report on what has happened to 99 children who were given fever therapy for their first attacks of chorea and most of their subsequent attacks, compared to 60 who did not receive this treatment. All of these patients were seen in the first attack, and most of them in recurrences. They were carefully followed, and the records give accurate and detailed information. The study of the effect of fever therapy on chorea was begun in 1930. The untreated patients were mostly seen before that time.

The purpose in making this analysis was to ascertain whether the course of the rheumatic infection was in any way different in the treated and untreated patients.

The first group is composed of 48 treated and 23 untreated patients whose observation period was one to three years. The second group is 51 treated and 37 untreated observed four to six years.

Table I gives the percentages of recurring chorea, polyarthritis, the development of heart disease, and deaths from heart disease in the two groups.

TABLE I

	TREATED (PER CENT)	UNTREATED (PER CENT)
Observed One to Three Years		
Chorea	31.5	37.5
Polyarthritis	6.0	32.0
Heart disease	12.5	26.0
Deaths from heart disease	2.8	13.0
Observed Four to Six Years		
Chorea	41.0	51.0
Polyarthritis	6.0	33.0
Heart disease	29.4	35.0
Deaths from heart disease	1.96	10.8

The most striking differences are the higher percentages of polyarthritis and deaths from heart disease in both observation periods among the untreated cases. The difference is so great and so similar in both periods as to seem significant.

With such a marked difference in attacks of polyarthritis it seemed inconsistent to find only a slight difference in the amount of heart disease.

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Therefore, the figures for heart disease were broken down to determine the severity of the cardiac lesions.

Figure 1* shows the result of this analysis. None of the treated cases observed one to three years developed aortic lesions, whereas one (4.3 per cent) of the untreated did. In the four- to six-year group one treated case (2 per cent) had aortic disease compared to six (16.2 per cent) in the untreated. Or, expressed differently, of those who developed organic heart disease in the one- to three-year group none of the treated cases had aortic disease compared to 16.6 per cent in the untreated. In the four- to six-year group 6.6 per cent of the treated group who developed heart disease had aortic lesions, compared to 46 per cent of the

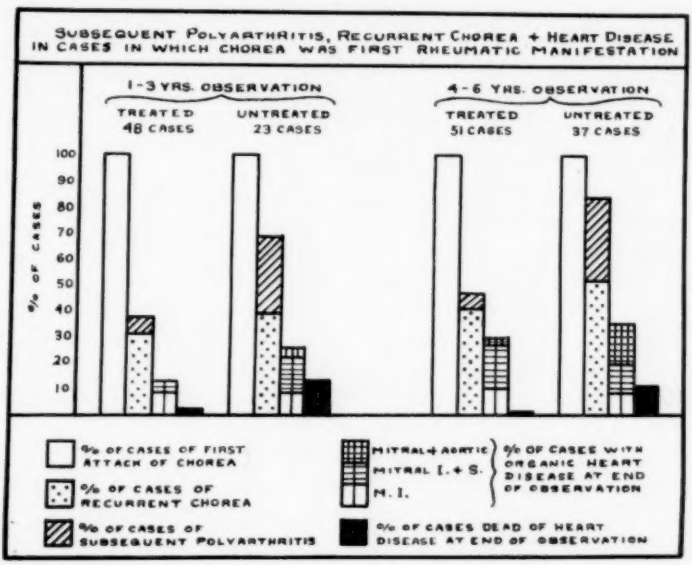

Fig. 1.

untreated. That is, although there is only a small difference in the amount of heart disease in both the treated and untreated patients, the stage of heart disease was considerably more advanced in the untreated than in the treated. This explains the higher proportion of deaths from heart disease among the untreated.

It may be suggested that since the severity of rheumatic infection appears to vary in different years a comparison of this sort should be made of patients seen in the same years. Two points might be brought out in answer. One is that chorea is at any time an evidence of a mild rheumatic infection. The other is that the second observation

*Figure 1 with interpretations appears in the Transactions of the First International Congress of Fever Therapy, now in press.

period was long enough so that if there were a difference in severity of the infection in different years the figures would not be consistent for the two periods.

We would like to emphasize that the findings presented here were not anticipated by us, nor even hoped for. If they are valid the reason may be that the infectious process is inhibited by fever, although it is curious that the effect should be more striking in the severer forms of rheumatic infection, that is, polyarthritis and carditis, than on the recurrences of chorea.

The number of records analyzed is not sufficiently large to warrant conclusions. However, the findings on the patients observed one to three years and four to six years are very similar and for that reason we think may be of some significance. We hope that others who are using fever therapy for chorea are following their patients carefully so that similar analyses can be made. If fever therapy does modify the course of rheumatic infection in those patients who receive it, it is a far more important therapeutic procedure in this disease than if its value is confined to shortening an attack of chorea.

We are indebted to Miss Claire Lingg and her staff of the New York Heart Association for analyzing our records.

A METHOD OF DIET ANALYSIS

Application in Research and Pediatric Practice

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DURING recent years there has been rapid extension of knowledge as to the rôles played by various nutrients in the processes of growth and development and in the maintenance of health. As a result, increased attention has been given to the effects of an abundance or lack of one or more of the food essentials upon children in various stages of the growth period. It is generally agreed that one of the requirements for optimal growth and development is an intake of sufficient amounts of the known dietary essentials to meet certain recognized requirements. The amount of each nutrient which is considered sufficient to provide for optimal growth and the maintenance of health is commonly referred to as the optimal dietary intake. This amount has been calculated from the results of balance studies and other experimental evidence, but the figure suggested is always intended to provide a liberal margin of safety. The accuracy of this estimate is undoubtedly greater in respect to certain of the nutrients than others. It is unlikely, however, that many of the present estimates will remain unchallenged after more extensive studies of the influence of varying amounts of these substances upon the growth and development of children have been completed. The requirement for any one of the food substances undoubtedly varies within a wide range in different individuals and under different circumstances.

Faulty metabolism may result in varying degrees of malnutrition in spite of an excellent diet, but a diet deficient in one or more of the essentials is usually found to have preceded malnutrition. It is becoming generally recognized that far too large a percentage of children suffer from the habitual consumption of suboptimal amounts of several of the essential nutrients.[1] While outspoken examples of the deficiency diseases are being encountered with less and less frequency, it is still common experience to find children in whom poor nutritional condition is suggested by physical examination, and this always raises the question of dietary inadequacy. Under these circumstances, the physician wishes to secure definite information as to the kinds and

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This article is being submitted in advance of the detailed reports of the studies in which the method was developed. A wide interest in obtaining more satisfactory methods of collecting and evaluating dietary information has become so apparent that the authors believe this should serve a useful purpose. The method as described has been used for more than five years at the Center for Research in Child Health and Development of the Harvard School of Public Health.

amounts of food which have been taken by the child in his average daily diet. In following normal children as part of general health service, it is also desirable to review each child's dietary from period to period in order to correct faulty habits. The need for a reasonably accurate and practical method for obtaining information becomes of prime importance when the various influences at play during the succeeding stages of growth and development are being considered in any research undertaking.

The authors have been following the growth and development of a large series of children from birth onwards at the Center for Research in Child Health and Development, established by the Department of Child Hygiene of the Harvard School of Public Health.* Many of the problems with which this research deals required continued and reliable dietary information as part of the history of each individual. It became necessary at the outset, therefore, to find a method by which satisfactory information could be obtained on repeated occasions concerning the diet of a child living under normal circumstances in his own home. Having determined upon a satisfactory method of securing this information, it became necessary to decide how these crude nutritional data could be analyzed and evaluated, both in respect to its consistency from period to period and in respect to the health and the growth of the child. The problem of analysis and rating was of particular importance because of the large number of children to be dealt with and the frequency of their dietary review.

It is fully appreciated that complete balance studies are necessary for accurate quantitative information as to the amounts of the individual nutrients which are consumed and the extent of their utilization by the body. However, balance studies are exceedingly time-consuming and costly and have thus far proved practicable only in certain intensive types of research covering relatively brief periods. This method was entirely unsuited to the project at the Center. Hence, a system was developed for recording and evaluating dietary histories. During the past six years, these histories have been obtained from the mother at regular intervals and have dealt with the maternal diet during pregnancy and with the child's diet from birth.

*This Center was established seven years ago for the purposes of comprehensive longitudinal studies of normal children from birth through a major segment of the developmental period. The growth and development of these children is being followed at specified ages by a number of workers representing various interests and disciplines. In addition to these data obtained by means of examinations, extensive histories are being accumulated through interviews dealing with the child's heredity and the various environmental forces which have played upon him. The dietary histories which are being reported represent only one phase of the total history. All children enrolled in this study have been entered by their mothers while attending the prenatal clinics of the Boston Lying-in Hospital, and the dietary history starts with a review of the mother's customary eating habits and any changes in these habits which have occurred during pregnancy. At the time of writing, the oldest child enrolled is 7 years of age, and the youngest only a few weeks. Two hundred and ninety-eight children have been enrolled, and two hundred and twenty-seven are still actively under study. This entire project has been described in considerable detail, but this description is still in manuscript form. It is anticipated that it will appear in the near future in the monograph series published by the Society for Research in Child Development.

It has been found that they afford an excellent opportunity to observe the effects which variations in diet may have on health and development in both prenatal and postnatal life. The experience with this technique at the Center has convinced the authors of its value to the student of growth and development. Its application over a long period to a large number of children should yield important information as to the rôles played by varying amounts of nutrients in determining the course of physical growth. It has also been felt that the pediatrician could apply this method, possibly in a modified form, to meet his own needs in connection with health services. He could secure in this way a far more accurate picture than he customarily obtains as to the food habits and daily food intake of his children. He could thus become aware of those changes in food habits from period to period which deserve attention, and of the extent of deviation of a particular child's diet from that which he considers optimum.

METHOD OF COLLECTING DIETARY INFORMATION

It is most important that information relating to a child's dietary be gathered by a nutritionist with adequate training and experience if the material collected is to be used for research purposes. Such a nutritionist could also be of real assistance to the physician both in the collection of accurate information and in corrective teaching. Experience shows clearly that the teaching of simple nutritional facts is greatly needed and, in most cases, appreciated by the mother. However, it is entirely possible for a pediatrician or his nurse to take a dependable nutrition history, provided he has familiarized himself with food values and has acquired a technique for appraising diet. If time does not permit the inclusion of thorough histories as a part of every interview, it is always possible to include at least a few leading questions regarding a child's eating habits. If this brief interview leaves any question as to the adequacy of a child's diet, arrangements should be made for a more detailed analysis. It is essential in taking complete dietary histories that sufficient time be provided for unhurried exploration of the range and amounts of foods eaten. The person taking the history must secure the confidence of the mother and use both tact in obtaining the desired information and judgment in determining its accuracy. For these purposes, appropriate nutrition forms are exceedingly helpful.

In connection with the nutrition studies being conducted by this department, a set of forms have been evolved for the recording of nutrition data. As space does not permit the presentation of all of these forms, two have been chosen to illustrate the method which has been adopted. The forms which have been omitted are for use at special periods, such as during pregnancy, lactation and in early infancy. The latter will be included in the monograph re-

ferred to in the preceding footnotes. The form presented in Fig. 1 is used by the nutritionist at each interview for recording the previous twenty-four-hour intake. This is done in the presence of the mother so that she may understand how a day's dietary should be recorded on this form. Three of these forms are then given to her, and she is asked to keep a complete record of the child's intake during three consecutive days. The forms which the mother provides in this way

HARVARD SCHOOL OF PUBLIC HEALTH
THE CENTER FOR RESEARCH IN CHILD HEALTH AND DEVELOPMENT

316 Longwood Avenue, Boston, Massachusetts

One Complete Day's Record of Food Eaten

Directions:

Orange juice or *fruit:* State number of oranges and size used.

Other fruit: State kind, number or size of serving (1 small sauce dish = ½ measuring cup, 4 rounding tbsps.* = ½ cup, 16 level tbsps. = 1 cup).

Cereal: State amount as rounding tbsps. or in terms of measuring cup.

Bread: State number of slices, and if purchased as sliced bread. If not, state thickness as ¼ or ½ inch or whatever it is.

Butter: Record as level tsps. (1 pat = 1 level tsp.†).

Egg: Check as to whether whole egg or yolk only.

Bacon: Number of slices—indicate whether long (full length) slices or ½ slices.

Milk: Amount on cereal—state in terms of measuring cup. If top milk or cream used, cross out milk. State cream light, medium, or heavy. Cup refers to measuring cup. *1 ordinary drinking glass = ¾ cup.* 1 tall glass (iced tea glass) = 1¼ cup. Where it states milk or cream, cross out one not used.

Sugar: Give as level tsps.

Other foods: Record as accurately as possible in ordinary household measures any foods eaten not listed.

Meat or Fish:

1 small serving meat or fish = 1 oz. = 2 tbsps.
1 average serving meat or fish = 3 oz.
1 large serving meat or fish = 4 oz.

Vegetables: Record in rounding tbsps.
(1 ordinary small saucer of vegetables = ½ cup = 4 rounding tbsps.)

Dessert:

Average serving = ½ cup.
Milk or sauce, etc., added should be recorded and amount stated.

*Tablespoon = tbsp.
†Teaspoon = tsp.

Fig. 1.

are used as a check upon the accuracy of the information which she gives the nutritionist directly at the time of interview. The second form, shown in Fig. 2, records the mother's impression of the average amounts of each of the different kinds of foods taken daily by the child. The amounts of the protective foods are recorded individually and in some detail. Information is obtained regarding the child's fondness or dislike for various foods, with note of any changes in this respect during the interval. Data pertaining to the child's eating habits and general dietary management are also recorded. While listing this information, the nutritionist attempts to explain by further

questioning any marked discrepancies between these different sources of information. This method of cross-checking has been found to add distinctly to the accuracy of the records.

METHOD OF EVALUATING DIETARY HISTORIES

Accurate and comprehensive tables of food values must be available for reference in evaluating dietary histories. The tables of Rose[2] and those of Bowes and Church[3] are both excellent and are used by us for

Name _____ **Date** _____

Address _____

Read directions carefully before filling out the following:

Breakfast: **Time**_____A.M.

Orange_____Amount. Other fruit_____Amount_____

Cereal—Kind _____ Amount_____

Bread—Kind_____ { No. slices_____ / Thickness_____inch } Toasted { Yes / No }

Butter—Amount_____tsps.

Egg_____No. whole egg or yolk. How cooked_____

Bacon_____No. of slices. Sugar on cereal_____tsps.

Milk_____Amount on cereal. Milk to drink_____cups

Cocoa _____cups. Other beverage_____cups

Is cocoa made with milk?_____If not, what part milk?_____

Sugar in cocoa or other beverage_____tsps.

Milk or cream added to cocoa or other beverage_____tbsps.

Other foods eaten_____Amounts_____

_____Amounts_____

Between Breakfast and Dinner

Foods eaten _____Amounts_____

_____Amounts_____

_____Amounts_____

(Include ice cream, candy, sodas, etc.)

Time_____A.M. Regular_____Irregular_____

Fig. 1.—Cont'd

this purpose. The nutritionist who is constantly calculating diets is able to judge the adequacy of a given diet without actually computing its composition. This presupposes considerable familiarity with food values and cannot be relied upon by others. A little practice in the calculation of diets, however, affords an excellent means of improving one's judgment of whether a diet is excellent, fair, or poor in respect to each essential. Diet records obtained at the Center are not calculated exactly in terms of grams of carbohydrate, fat, protein, calcium, phosphorous and iron, but are estimated on the basis of the amounts of those foods in the diet which are excellent or good sources

of each of these nutrients. Likewise, vitamins are not expressed in units but are rated in terms of amounts of excellent or good sources.*

In order to express the values arrived at in a brief and clearly understandable way, a five-point rating scale has been used. Five-plus or *excellent* indicates that a nutritional essential is present in

Dinner (Midday Meal)_____**Hr.**

Soup_____Kind. Amount_____

Meat, egg, fish or substitute_____Kind. Amount_____

Potato—No. and size_____How cooked_____

Skin eaten_____

Cooked vegetables_____Kind. Size of serv._____

_____Kind. Size of serv._____

Raw vegetables_____Kind. Size of serv._____

_____Kind. Size of serv._____

Bread: Kind_____ { No. slices_____ / Thickness _____ inch

Amount of butter used on bread, potato, vegetable_____tsps.

Amount of salad dressing and kind_____tsps.

Amount of gravy_____tbsps.

Milk: Amount_____cups Other beverage _____cups

Sugar in beverage_____tsps. Cream or milk_____tbsps.

Dessert: Kind_____ Size of serving_____

Other foods eaten_____ Amounts _____

_____ Amounts _____

_____ Amounts _____

Between Dinner and Supper

Foods eaten_____ Amounts _____

_____ Amounts _____

_____ Amounts _____

(Include ice cream, candy, sodas, etc.)

Time_____P.M. Regular_____Irregular_____

Fig. 1.—Cont'd

an amount at least equal to the generally accepted nutritional requirement termed "optimum."[4] When rated four-plus or *good,* the food essential under consideration has been present in reasonably satisfactory amounts, although somewhat less than the generally accepted

*As an illustration of this method of evaluating a particular nutrient, let us take the simple example of calcium in the diet of a 2-year-old child. The diet at that age must contain 1 gm. of calcium daily to be given an excellent (five-plus) rating, according to our standards. The average daily diet taken by this child contained the following excellent or good sources of calcium:

Milk	22 oz. daily (all sources)
Vegetables	2 tablespoons daily (leafy green twice a week)
Fruit	1 orange daily—other fruit 2-3 times a week
Egg	3-4 times a week

In this instance, milk, the only excellent source of calcium in this diet, furnishes approximately three-fourths of the desired amount, and the remaining foods are not sufficiently good sources to provide a full additional 0.25 gm. The calcium is, therefore, rated four-plus or good. A similar procedure is followed for each essential nutrient, some of which obviously present a more complicated picture.

optimum. A three-plus or *fair* rating has been used to indicate that although the diet is not good as to the amount of the nutrient under discussion, a considerable proportion of the desired total is still present. Such a rating in clinical practice calls for advice as to improvement. A two-plus or *poor* rating indicates that the diet is definitely unsatisfactory in this particular, and efforts should always be made

Supper (Evening Meal): **Time**_____P.M.

Main Dish: Kind_____ Amount _____

Potato: No. and size_____ How cooked_____

Skin eaten_____

Vegetables: Cooked: Kind_____ Size of serv._____

Raw: Kind _____ Size of serv._____

Bread: Kind_____ { No. slices_____ / Thickness _____inch

Amount of butter used on bread, potato, vegetables, etc._____tsps.

Salad dressing: Kind_____ Amount _____

Gravy _____tbsps

Milk: Amount_____cups Other beverage _____cups

Sugar in beverage_____tsps. Cream or milk_____tbsps.

Dessert: Kind _____ Size serving_____

Other foods eaten_____ Amounts _____

_____ Amounts _____

Between Supper and Bedtime

Foods eaten_____ Amount _____

_____ Amount _____

_____ Amount _____

(Include ice cream, candy, sodas, etc.)

Time_____P.M. Regular_____Irregular_____

Cod Liver Oil_____tsps. No. times daily_____

or

Substitute _____drops

Water: No. of glasses daily_____

Appetite, less than usual_____usual_____

more than usual _____

Sickness or indisposition, specify_____

_____

Remarks:

Fig. 1.—Cont'd

to secure correction. A one-plus or *very poor* rating indicates gross inadequacy. This five-point rating scale has been adopted in part because it does not suggest greater accuracy than the history justifies, nor does it convey dogmatic implications in respect to our present nutritional standards. Each of the five ratings may be defined in terms of any nutritional standards chosen by those using the method, but the definitions adopted must be followed with as great consistency as possible.

A rating of the whole diet for any given interval, while not as definite or accurate as the ratings for each nutrient, nevertheless has been found helpful in comparing a child's diet at different age periods, or in placing it in relation to the diets of other children. No diet is

DIET RECORD
(After Formula Period)

Name_____ **Date** _____

No._____ **Age** _____

Answers represent usual or average occurrences during preceding_____months.

Meal Hours: Breakfast_____ Dinner_____ Supper_____

Other feedings_____ Time spent at each meal_____min.

Are meals regular in time_____usual type meal_____surroundings_____

Appetite usually excellent_____good_____poor_____variable_____

Child's general attitude toward food: finicky, dawdling, interested_____

Other habits _____

Family often resorts to: forcing, coaxing, bribing, scolding, substituting other foods.

Other practice _____

		Child's Reaction to
Milk	Total amount daily (cups)_____	_____
Other fluids	(water, soup, etc.) Total amount daily (cups)_____	_____
Eggs	Number per week_____	_____
Cereals	Kinds _____	_____
	Times per week____ tbsps. at time____	
Bread	Kinds _____	_____
	Number of slices per day_____	
Fruits	Oranges Times per week_____	_____
	Other kinds _____	_____
	Times per week_____	
Vegetables	Kinds _____	_____
	Times per day_____ tbsps. at time_____	
	Raw vegetables _____	_____
	Green leafy vegetables_____	_____
Potatoes	Method of cooking_____ Amt. daily_____	_____
Butter	Number of tbsps. daily_____	_____
Meat or Fish	Kinds _____	_____
	Times per week____ tbsps. at time____	
C.L.O. (or substitute)	No. tsps. daily____ drops daily____	_____
	Candy_____ Ice Cream_____	
	Tea_____ Cocoa_____Coffee_____	
	Other food at meals_____	
	_____	
	Food between meals_____	
	_____	

Remarks:

Fig. 2.

considered five-plus or *excellent* unless it can be said to meet that standard for all the nutritional essentials. Few diets meet this level, although a considerable number are rated four-plus or *good*. The latter are usually excellent in some of the essential food substances, good in others, possibly only fair in one respect. A three-plus or *fair* diet may be found to be *excellent* or *good* in some respects, but only *fair* in its provision of other essentials. It may possibly be *poor* in

one respect but is never *very poor* in any particular. A diet rated two-plus or *poor* will usually be found *poor* in several essentials. A one-plus or *very poor* diet will be found to be either *poor* or *very poor* in many if not all of the food essentials.

ILLUSTRATIONS OF THE APPLICATIONS OF THIS METHOD OF DIET ANALYSIS

Those interested in the application of this method to the study of individual children are referred to the monograph which already has been mentioned. In this monograph the case histories of six children are presented in considerable detail. They represent two families, formed by the marriage of sisters, each of whom has thus far enrolled three children for continuous study from the time of birth. The nutrition records on these children are, therefore, quite complete and cover a period of six and one-half years in the case of the oldest child. They afford an interesting opportunity to compare the dietary evaluations of each child with his health experiences and growth progress, as well as with the diets and other findings of his siblings and cousins at comparable ages. It has not been possible to study all the records in the files of the Center in this detail. Certain features, however, of the growth patterns of these six closely related children, and others who have been studied in some detail, are in agreement with the pictures which might be predicted from the study of their dietary patterns.

The hemoglobin readings obtained from a group of children of the same age may be taken as one measure of the adequacy of their diets, in respect to iron at least. The children on whom the dietary ratings were available for the age interval eighteen months to two years have been ranked according to the levels of their hemoglobin at the two-year examinations. The ten children showing the highest hemoglobin readings were compared with the ten showing the lowest readings at this age. The data presented in Tables I and II show the correlation between independently evaluated dietary iron and hemoglobin levels in these two groups of children. They present in addition the red blood cell counts and a statement of other factors culled from the medical records which it was thought might have influenced the hemoglobin levels. The red blood cell counts show a poorer correlation with diet than do the hemoglobin readings, but there is a tendency to follow in the same direction. There are no five-plus or *excellent* ratings for dietary iron in either group. This is not surprising, as iron is one of the nutrients most often inadequately supplied in the diet according to the standards which have been accepted for this appraisal. The highest hemoglobin level, 13.5 gm., was presented by Case 147. This child also had a high red cell count and a good rating for dietary iron. The only other case with an equally good dietary rating (Case 256) shows a lower hemoglobin, but this child had two infections between eighteen months and two years of age. The only apparent discrepancy in this table is presented by Case 140, in which the diet had been

given a *poor* rating. It is of interest that a review of the history shows that the accuracy of the nutrition information had been questioned, and a note entered to the effect that this child *probably* ate an unusually large amount of chocolate. A large amount of chocolate would appreciably increase the intake of iron. Table II, on the other hand, shows that among the children with the lowest hemoglobin values, all but two had had diets for the interval considered *poor* in respect to iron. In two cases a three-plus or *fair* rating was given for iron intake. In one of these (Case 240) the medical history records frequent colds during the interval, and in the other (Case 223) there had been an attack described by the mother as "grippe."

TABLE I

THE TEN HIGHEST HEMOGLOBIN LEVELS AT TWO YEARS

CASE NO.	DIETARY IRON RATING	HEMOGLOBIN (GM.)	R. B. CELLS (MILLIONS)	OTHER FACTORS
256	Good	12.3	5.1	Two infections
211	Fair	13.2	4.9	
162	Fair	12.3	5.1	
147	Good	13.5	5.4	
140	Poor	13.2	5.1	Accuracy of dietary history questioned when taken
132	Fair	12.9	4.4	
222	Fair	12.7	4.8	
145	Fair	12.3	4.8	
126	Fair	12.4	3.9	
157	Fair	12.2	5.5	

TABLE II

THE TEN LOWEST HEMOGLOBIN LEVELS AT TWO YEARS

CASE NO.	DIETARY IRON RATING	HEMOGLOBIN (GM.)	R. B. CELLS (MILLIONS)	OTHER FACTORS
163	Poor	10.1	4.2	
159	Poor	10.2	5.3	
240	Fair	9.9	4.3	Frequent "colds"
254	Poor	10.0	4.5	
232	Poor	9.5	4.4	
233	Poor	9.8	4.6	
223	Fair	9.7	4.6	Attack of "grippe"
181	Poor	10.0	4.4	
201	Poor	10.0	4.3	
121	Poor	9.8	4.3	

In studies on pregnant women by Teel, Burke, and Draper, at the Boston Lying-in Hospital, a comparison has been made between the intake of vitamin C and the average values for ascorbic (cevitamic) acid in the blood during pregnancy.[5] In approximately one hundred instances the vitamin C intake was evaluated independently from the maternal dietary history. At the same visit the ascorbic acid level in the blood plasma was determined. In forty-six instances in which the diet was rated five-plus or *excellent* in respect to vitamin C, the average value for ascorbic acid was found to be 0.96 mg. per cent. In

twenty-six instances in which the dietary intake of vitamin C was considered three-plus or only *fair*, the average value for ascorbic acid was 0.57 mg. per cent. In twenty-seven cases in which the intake of vitamin C was rated as *poor* or *very poor*, the average value for ascorbic acid was 0.23 mg. per cent. This correlation is evidence that the information obtained from these women and the ratings deduced therefrom, were significant with respect to vitamin C.

SUMMARY

Balance studies are impractical as a means of studying the nutrition of groups of children living under reasonably normal circumstances. This is especially true when it is necessary to follow changes in diet over a number of years. Dietary histories can serve certain research purposes with considerable satisfaction if taken by properly qualified persons and if certain precautions are followed.

A technique has been described for obtaining such histories and for evaluating them without resort to elaborate mathematical calculations. This method of approach is not new. It is believed, however, that the technique which has been developed for its application has contributed to the reliability of the data recorded and to the consistency of the ratings. The significance of this method of evaluation, as expressed in the five-point scale, is readily appreciated. More detailed assessment of the records is probably not justified by the nature of the information which they contain.

This technique has been found of great assistance in the studies being conducted at the Center for research at the Harvard School of Public Health. Examples of the application of the method to the study of nutritional differences between children and between pregnant women have been presented and show that a correlation exists between the dietary ratings and the objective measures of various nutritional states.

A modification of this technique of dietary study could unquestionably be applied in pediatric practice. The casual method of inquiring about a child's diet, commonly relied upon by physicians, is not sufficient to justify conclusions as to whether a diet is or is not adequate in its provision of all essentials. The adoption of a simple but sufficiently accurate method of diet analysis, such as the one described, would lead to a wider and more exact appreciation of the present knowledge of nutrition in its application to preventive medicine.

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THE TREATMENT OF MENINGITIS DUE TO HEMOLYTIC STREPTOCOCCUS WITH SULFANILAMIDE

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TORONTO, ONTARIO

THE following communication presents the results of the treatment of nine patients suffering from meningitis due to hemolytic streptococcus with sulfanilamide. No attempt is made to review the extensive literature on the subject of sulfanilamide therapy.

CLINICAL DATA

From 1924 to 1936, ninety-three patients suffering from meningitis due to hemolytic streptococcus have been admitted to the Hospital for Sick Children, Toronto. This series of cases was treated either by spinal drainage, intravenous glucose-saline injections, scarlet fever antitoxin, and mastoidectomy when it was indicated, or by some combination of these methods. In this group of cases there was one recovery. From this patient a culture of hemolytic streptococcus was obtained from the cerebrospinal fluid on only one occasion. The treatment used in this case was daily spinal puncture and drainage. During 1937 nine cases of streptococcic meningitis have been treated with disodium-4-sulphamidophenyl-2-azo-7-acetyl-amino-1-hydroxynaphthalene 3:6-disulphonate (prontosil) and para-aminobenzenesulphonamide (prontylin) or both, as well as with a continuous intravenous injection of glucose-saline, daily spinal puncture with drainage, and mastoidectomy in patients suffering from mastoid disease. Table I summarizes the results obtained.

COMMENT

Probably the most efficient test of a therapeutic agent is to observe its effects in patients suffering from a disease which usually has a case fatality of from 95 to 100 per cent. Before the use of sulfanilamide, of a total of ninety-three patients with streptococcic meningitis in our series, only one recovered. The recovery of this patient may not have been unusual since on only one occasion was a culture of the spinal fluid reported positive. In our series of five recovered patients, four showed the presence of hemolytic streptococcus in culture from the spinal fluid on three or more occasions. Previously such cases treated by other methods, in our experience, have resulted fatally. Although, as stated in an article on influenzal meningitis,[1] continuous intravenous injection of fluids facilitates more adequate spinal drainage, we believe that the use

From the wards and laboratories of the Hospital for Sick Children, Toronto, the Department of Paediatrics and the Connaught Laboratories, University of Toronto.

TABLE I

SUMMARY OF HISTORIES OF PATIENTS WITH STREPTOCOCCIC MENINGITIS

	PATIENT	AGE	SEX	SOURCE	NUMBER OF CONSECUTIVE DAILY POSITIVE CEREBROSPINAL FLUID CULTURES	TREATMENT	RESULT
1.	R. B.	19 mo.	M	Blood stream	4	Continuous intravenous Prontosil 38 c.c. I. T.* in 4 days Prontosil 60 c.c. I. M.† in 4 days	Died
2.	G. P.	12 mo.	M	Otitis media Blood stream Skin	2	Continuous intravenous Prontosil 45 c.c. I. M. in 3 days Prontylin 10 gr. by mouth for 1 day	Died
3.	S. H.	5 yr.	M	Mastoid Extradural abscess	4	Continuous intravenous Prontylin 310 gr. in 9 days Mastoidectomy drainage of abscess	Recovered
4.	J. T.	9 yr.	M	Mastoid	3	Continuous intravenous Prontosil 385 c.c. I. M. in 8 days Prontylin 110 gr. by mouth in 7 days Mastoidectomy	Recovered
5.	S. J.	5 yr.	F	Mastoid	4	Continuous intravenous Prontylin 500 gr. by mouth in 6 days Mastoidectomy	Recovered
6.	R. H.	10 yr.	M	Mastoid	1	Continuous intravenous Prontylin 220 gr. by mouth in 3 days Mastoidectomy	Recovered
7.	B. Y.‡	5 yr.	M	Mastoid	3	Continuous intravenous Prontylin 520 gr. by mouth in 16 days Mastoidectomy	Recovered
8.	E. L.	2 yr.	F	Mastoid	2	Transfusion Continuous intravenous Prontylin 240 gr. by mouth in 2 days Mastoidectomy	Died
9.	R. L.	3 yr.	M	Mastoid	7	Continuous intravenous Prontylin 270 gr. by mouth in 5 days Mastoidectomy	Died

*I.T. signifies intrathecal.
†I.M. signifies intramuscular.
‡Case 7—reported with the permission of Dr. Bradley.

of sulfanilamide in patients with streptococcic meningitis, secondary to mastoid disease, was mainly responsible for their recovery. In the group of nine cases it may be significant that the four patients who died were the youngest of the group. In addition to meningeal involvement there was a septicemia in two of them. It is our belief that the use of sulfanilamide has not favorably affected the most critically ill patients. There were no alarming effects produced as a result of the administration of the drug. Cyanosis was noted in all of our patients receiving prontylin in large doses, but this subsided within a few days after the drug had been discontinued. An increased respiratory rate was noted occasionally, but it was not a disturbing symptom. There have been no sequelae in four of the patients whom we have been able to reexamine. Dr. Frieda Fraser of the Connaught Laboratory has examined four of the cerebrospinal fluid strains isolated and found that they are all hemolytic streptococci of group A (Lancefield).

SUMMARY

1. From 1924 to 1936, ninety-three patients suffering from meningitis due to hemolytic streptococcus have been admitted to hospital. These patients were treated by one of the following procedures, or by a combination of them: namely, spinal drainage, intravenous glucose-saline injections, scarlet fever antitoxin, and mastoidectomy when indicated. In this group there was only one recovery.

2. Nine patients with streptococcic meningitis during 1937 have been treated with sulfanilamide, a continuous intravenous injection of glucose-saline and daily spinal puncture with drainage. Mastoidectomy was performed in six of the nine patients in whom mastoiditis was present. Five of these nine patients have recovered.

3. It is our belief that sulfanilamide has been chiefly responsible for the satisfactory outcome in our patients suffering from streptococcic meningitis secondary to mastoid disease.

The authors wish to thank the staff of the Ear, Nose and Throat Service of the Hospital for Sick Children for their cooperation, assistance, and suggestions in the treatment of these patients. Also we are indebted to Dr. Bradley of this service for permission to include Case 7 in our series. We also wish to thank Dr. Leonard Colebrook for his help and suggestions in the treatment in Case 3.

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POLIOMYELITIS OCCURRING TWO YEARS AFTER VACCINATION AGAINST THE DISEASE

Report of a Case

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In 1934, Kolmer[1] announced a new vaccine believed capable of producing active immunization against acute anterior poliomyelitis. Because of the devastating and serious nature of this disease, a country-wide interest was immediately aroused. The public soon learned of the vaccine and, in turn, there was a prompt nation-wide demand on the part of parents to protect their children against the disease.

Before attempting to use the vaccine on any children, Dr. Kolmer had courageously administered it to himself, to his assistant, and to his two sons, without any harmful effects. It should be remembered, out of due consideration to him, that at the time Kolmer expressed hesitation in advising the injection of a vaccine known to contain living virus, but he believed it a safe and effective method for vaccination against acute anterior poliomyelitis, given according to his directions, if judged from the results observed on himself and his assistant, his own children, and vaccinated monkeys. Nevertheless, a year later, after further studies and experimentation he stated, "Great encouragement is given to efforts for producing a safe and effective method for the vaccination of human beings against the disease."[2]

Meanwhile, beginning in April and extending through September, 1935, the Kolmer vaccine was given to 10,725 individuals.[3] Almost at the same time research workers in the field of poliomyelitis immunization questioned the safety and effectiveness of this particular vaccine. At the meeting of the American Public Health Association at Milwaukee early in October, 1935, after a vigorous discussion, the consensus of opinion was that "the value of the poliomyelitis vaccines was strongly deprecated."[4]

Flexner,[5] writing on this subject, warned against the use of vaccines and pointed out its potential danger. He stated, "No adequate evidence has been presented showing that through the action of physical or chemical agents the virus of poliomyelitis may be deprived of its potential paralyzing power."

In December of the same year, Leake,[6] Medical Director of the United States Public Health Service, reported twelve cases of paralytic poliomyelitis following injection of the two types of treated poliomyelitis virus being used that year with the hope of establishing acquired

immunity against the disease. He did not specify whether or not Kolmer's vaccine had been used. All these cases reported by him occurred from six to fourteen days after the use of the vaccine, and in six cases the patients died. He explained, "Although any one of these cases may have been entirely unconnected with the vaccine, the implication of the series as a whole is clear."

At about the same time Kolmer himself[7] made the statement that no one receiving the three doses of the vaccine had developed the disease but there had been ten instances of poliomyelitis developing after one or two doses of the vaccine and it appears reasonably certain that some, if not all of these, had been instances in which the vaccine was given during the incubation period too late to abort the disease.

It is recalled that so strong were the unfavorable arguments and criticism that the use of the vaccine was brought to an abrupt halt. Paralytic poliomyelitis with high fatality was cited as resulting from the sodium ricinoleated preparation. Five deaths occurred following its use under conditions that clearly incriminated the vaccine. Official action was taken by the United States Public Health Service, the authorities holding that the fundamental tenets on which its use was based were scientifically unsound.[8]

First of all, it was demonstrated that immunity may be present even in the absence of antiviral antibody in the blood. The exact site of the natural immunity is undetermined, but facts suggest that it lies within the nervous tissues. There was evidence that paralysis could occur even when neutralizing substances were present in the blood during the preparalytic and early paralytic days of the disease in humans. This is understandable if we bear in mind that the central nervous system is separated by a filtering process from all other parts and systems of the body, even from the blood. However, the cells and tissues in themselves are believed to be capable of independent immunity. Stress has been laid upon the significance of this fact in considering the complexities of poliomyelitis immunity. Furthermore, experiments have been carried out showing that the antiviral substance occurring in the blood appears to be capable only of neutralizing but not necessarily destroying the virus of poliomyelitis and that the presence of antibodies alone is not a measure of immunity. That "true, acquired active immunity to this disease is basically a cellular and not a humoral phenomenon" was pointed out by Schultz and Gebhardt.[9]

The efficacy of the vaccine was further questioned by Olitsky and Cox,[10] who drew certain important conclusions from their studies. The results obtained from their experiments on active immunization against experimental poliomyelitis indicate that "poliomyelitis virus treated with tannin, sodium ricinoleate or formalin does not constitute a satisfactory immunizing agent in monkeys against the experimental disease."

Rivers[11] criticized Kolmer for making the basic claim for safety of his vaccine dependent upon the fact that it is prepared from poliomyelitis virus derived from remote monkey passage, and further attenuated by contact with sodium ricinoleate and phenyl-mercuric-nitrate. A statement that poliomyelitis virus of monkey passage is less infectious for humans than is the natural or human virus is an assumption without experimental evidence to substantiate it.

It is of relevant interest to note that Kramer and Grossman,[12] in experimenting on a group of monkeys with poliomyelitis virus previously treated with 1 per cent sodium ricinoleate, found that the substances did not successfully attenuate the organism.

Aycock and Hudson,[13] after an experimental study on a group of children, also expressed doubt of any actual increase of immunity resulting from injections of attenuated poliomyelitis virus.

More recently Harmon and Harkins[14] reported on the relationship between the antiviral antibody content of the blood and parallel immunity, and questioned the fact that the virus-neutralizing substances in the blood were an accurate index of immunity against this disease. They concluded that no relation seems to exist between poliocidal bodies in the blood, and resistance and susceptibility to an attack of the disease.

Further doubt regarding the real protective value of these artificially produced humoral neutralizing substances present in the blood was expressed by Schultz.[15] In those animals naturally refractive to poliomyelitis, this endowed power does not appear related to humoral antibodies, for the serum of such animals rarely inactivates the poliomyelitis virus in vitro, even when a high ratio of serum to virus is employed. On the contrary, the natural protective activity appears to rest wholly, or largely, on tissue resistance.

Aycock and Hudson[16] also point out, "That the presence of this neutralizing substance may not actually constitute protection is suggested by the fact that the experimental production of neutralizing substances does not necessarily confer resistance to intracerebral inoculation or even intranasal instillation of the virus."

The entire status of the use of attenuated virus as a preventive measure against poliomyelitis is very ably summed up by Toomey.[17] He says, "First, artificial immunity may be established against poliomyelitis if the living virus is injected as the antigen; second, many monkeys acquire the disease during the process of active immunization. Vaccine antigens must be safe, thus they cannot be viable, and paradoxically, if they are not viable they seem to be of no value." It seems, therefore, that the procedures designed in an attempt to attenuate poliomyelitis virus to render it harmless and yet to retain its properties as a prophylactic vaccine have hitherto not been successful and the problem remains an unsolved puzzle.

Evidently, most investigators doubt the effectiveness of attenuated poliomyelitis virus as a prophylactic agent. Indeed, general opinion supports the contention that its clinical use should be considered dangerous or, to say the least, unsatisfactory. However, it would seem that interest should be centered chiefly in discovering whether or not such a vaccine really possesses potent antigenic power and is actually capable of producing active immunity against the disease in a human being. For this reason, the following case is reported in which a child, two years after receiving the Kolmer vaccine, developed a severe paralyzing poliomyelitis.

CASE REPORT

M. W., male, aged four years, was taken sick on July 26, 1937. Late that afternoon he vomited and had diarrhea, giving the impression of a gastrointestinal upset. Later he complained of pain in his back. His temperature, taken by the mother, was 103° F. Throughout the night he was feverish, extremely restless, and cried out as though in pain. The following day he complained of occipital headache, increasing pain in his back, pain in both legs and also called attention to the fact that they felt cold. At this point he was brought in for examination.

His previous history other than recurrent attacks of tonsillitis and otitis media is not significant. He has not had any of the acute exanthematous febrile diseases, whooping cough, or other common childhood illnesses. In fact, his record of health was very good. He had been immunized against diphtheria and also vaccinated against smallpox.

In reference to the immunization against poliomyelitis, this was undertaken on July 30, 1935, the child receiving the first dose of Kolmer vaccine on that day, the second a week later, and the last two weeks later. The dosage advocated for children of standard weight (0.06 to 0.1 c.c. per kilogram of body weight) was given: the first dose being 0.25 c.c.; the second, 0.5 c.c.; and the third, 0.5 c.c. Precautions had been taken for proper storage of the vaccine.

Physical Examination.—A white boy, very well nourished, appearing quite toxic, and sweating profusely, was acutely ill. The corneae and sclerae were glazed, and there was circumorbital puffiness. He was drowsy and stuporous but could be easily aroused. When disturbed for examination, he became extremely irritable. His outstanding complaint was pain in the back of the head and in his back. Attention was instantly focused on his spine, for he seemed to have difficulty in attempting to sit up. Disinclination to flex the spine was easily elicited, and pain and rigidity in this region were readily verified. The characteristic Amoss sign was evident as he attempted to raise himself to assume the upright position. Rigidity of the neck was marked. Movements of the upper extremities were accompanied by obvious tremors. He resented being disturbed and handled during the examination, apparently suffering intense pain, and seemed more comfortable when lying quietly. In addition to the obvious hyperesthesia, he was constantly whimpering and fretful. There was a complete flaccid paralysis of both lower extremities. The limbs fell like dead weights when lifted and were cold to the touch. On both sides the patellar reflexes were absent. The Achilles reflex was absent; the patellar clonus and ankle clonus could not be elicited. The Babinski phenomenon was not present, nor was the Oppenheim sign obtainable. The Kernig sign was negative. The abdominal and cremasteric reflexes were diminished and unequal. The bladder and rectal sphincters were uncontrolled. The upper extremities seemed to have been spared.

The oropharynx was hyperemic, the tongue heavily furred and dry. There was no cervical lymphadenitis. The left eardrum showed a perforation of long standing. The configuration of the chest was normal. The heart was not enlarged, and there were no murmurs. The lungs were clear. Liver and spleen were not enlarged. There were no palpable masses in the abdomen. The genitals were normal in appearance.

The diagnosis was acute anterior poliomyelitis.

Because of the nature of the illness he was transferred to the Essex County Isolation Hospital. On admission to this institution the diagnosis was confirmed. The temperature was now found to be 102° F., the respiratory rate 40, and the pulse rate 130. A lumbar puncture was performed and about 30 c.c. of cerebrospinal fluid under increased pressure were withdrawn, which was slightly like ground glass in appearance.

Laboratory Data.—The examination of the cerebrospinal fluid showed 152 cells per cubic millimeter, of which 95 per cent were lymphocytes. Globulin was absent. Sugar was 55 mg. per 100 c.c.; and the chlorides, 730 mg. per 100 c.c. This fluid on culture was negative for microorganisms, and the Levinson differential precipitation test was also negative.

Blood count: Leucocytes, 6,350; polymorphonuclear cells, 77 per cent; lymphocytes, 14 per cent; monocytes, 9 per cent, and band forms, not present. No erythrocyte count was done, and the hemoglobin was not estimated.

Urinalysis showed an acid urine having a specific gravity of 1.020; negative for albumin, glucose, and acetone. Microscopic findings revealed 16 white cells per high power field.

Course of the Disease.—During the stay in the hospital the temperature dropped through lysis. No further increase in paralysis was noted, with the possible exception of involvement of some of the muscles of the back. The child was kept in the hospital until August 20. Examination on that day revealed some return of motion in the limbs, more favorably in the left leg. The muscle tone had improved. The temperature was 100° F., the pulse 110, and the respiratory rate 25. His general appearance was excellent. He was able to sit up in bed and seemed bright and cheerful. He had regained control of the sphincters and was encouraged about being able to begin to move his toes and bend his left knee. He was removed to an orthopedic hospital for further treatment.

COMMENT

An assertion by Kolmer[18] is significant, namely, that it was not possible to state the duration of immunity following vaccination but that monkeys vaccinated three years previously were still immune to intracerebral injections of the virus. In the case herein reported only two years elapsed between the time of the vaccination and the development of paralytic poliomyelitis. Thus, if any immunity had been produced, it had disappeared during this time. Hope of immunizing against this disease by the vaccine method, therefore, does not seem promising, bearing out the opinions of research workers in the field, according to the references cited.

Of the 10,725 persons who received Dr. Kolmer's vaccine in 1935, none have been reported as developing poliomyelitis after a considerable lapse of time, with the exception of the case reported here. No instance has come to the attention of the United States Public Health Service, the New Jersey State Department of Health, or Dr. Kolmer, with all of whom I corresponded concerning this case.

Let us bear in mind in this connection, however, that no method of vaccination is 100 per cent perfect. Certainly this is true of diphtheria, scarlet fever, rabies, typhoid fever, and even smallpox.

In regard to the possibility of creating resistance by artificial means, certain facts are worth pointing out. From the reports of the many investigators engaged in poliomyelitis research, it seems quite clear that all the response one can expect from injections of attenuated poliomyelitis virus appears to be chiefly humoral in nature and not any genuine specific increase in tissue resistance. They agree almost uniformly that this artificial production of neutralizing antibodies in the blood does not necessarily confer immunity on the individual. That the true significance of humoral antibodies lies merely in producing adventitious by-products of infection seems clearly established. Furthermore, in Schultz's opinion,[15] the real basis of immunity is not humoral in nature but rests entirely, or largely, on cytoplasmic modification of previously susceptible neurons. This author explains the failure of humoral antibodies in the blood to protect against the disease as due to the fact that the virus normally gains entrance to the central nervous system by way of the olfactory nerves. The terminals of these nerves lie free on the nasal mucosa and therefore probably are out of reach of these substances circulating in the blood and cannot be affected by them. It is also known that when the virus has been subjected to the action of various physical or chemical attenuating agents in an effort to make it safe for human use, even the humoral response obtained from such a vaccine is weak, to say nothing of the failure to increase tissue resistance.

A review of the literature and the evidence of the case reported seem to verify Aycock's comment[19] on the use of the vaccines employed in the summer of 1935, with respect to their effectiveness as a preventive measure against poliomyelitis. His opinion is that they were recommended for human use on what appears to have been inadequate experimental evidence, both as to safety of the preparation and their ability to produce immunity.

We thus see that the attempt to induce active immunity by injections of attenuated poliomyelitis virus is a doubtful possibility. Furthermore, the method is to be considered highly experimental and not free from danger.

SUMMARY

According to the literature many adverse facts on the use of poliomyelitis vaccine have been established by investigators.

The case of a four-year-old boy who developed severe paralytic poliomyelitis two years after receiving Kolmer's ricinoleated poliomyelitis vaccine, in the dosage prescribed by Kolmer, is reported.

It verifies the consensus of opinion that the use of the vaccine is of doubtful value as a protective measure against poliomyelitis.

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DEATH OF A CHILD FOLLOWING ARTIFICIAL FEVER THERAPY

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THE purpose of this case report is to direct attention to the dangers inherent in artificial fever therapy. Fatalities are not infrequent as a result of its use. Anson and Clark[1] declare that the hazards of this type of treatment are too little appreciated. Kretchmer[1] in discussing fever treatment of gonorrhea, while admitting the brilliant results frequently achieved, advocates the exercise of extreme caution in undertaking treatment of this infection by this method. Hartman and Major[2] report the autopsy findings in two cases. In one, death occurred in a white woman of twenty, two days after the third weekly treatment administered for salpingitis. The second patient was a male of forty who died twenty hours after the completion of the eleventh treatment. Stuhler[1] reports one death in 125 cases treated at the Mayo Clinic. Ormond[1] reports one death and mentions two others that came to his knowledge. O. A. Nelson[1] records one death in 30 treated cases: a woman of thirty-two with death from shock within twenty-four hours following the first treatment, in the course of which the maximum temperature attained was 105.5° F.

CASE REPORT

The child whose case we are about to record was one of 25 patients treated up to May 15, 1937 at the Denver General Hospital by means of the General Electric inductotherm. Six were girls from two to ten years of age, five of whom were treated for gonorrheal vaginitis and one for chorea. The remainder were adults from twenty-two to sixty years of age. In addition to the death of the child herein reported, a fatality also occurred in a male of fifty, treated for gonorrheal urethritis. In two of the 25 patients, treatments were discontinued because of the severity of reactions. All suffered from nausea, vomiting, restlessness, and debility. The number of treatments ranged from one to eleven, with an average of three to four treatments per patient. The conditions for which treatment was administered were: gonorrheal urethritis, gonorrheal arthritis, salpingitis and epididymitis, chorea, asthma, and nonspecific arthritis. Each child had received one of the barbiturates and the adults morphine, for the control of restlessness and mental anxiety. Fever was maintained on an average for six hours, with the

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Acknowledgment is herewith cordially made to Dr. R. I. Bump, resident in pediatrics, for details concerning the patient.

temperature level at 105 to 106°. In the gonorrheal patients the fever range was 105 to 107° and in asthmatics and nonspecific arthritic patients 104 to 105°. All the usual precautions calculated to insure the safety of the patient were rigidly and scrupulously enforced. Treatments were administered by thoroughly trained technicians.

D. W., a two-and-one-half-year-old female of American parentage, was admitted to the Denver General Hospital April 26, 1937 with acute gonorrheal vaginitis of about five days' duration with no dysuria. The infection was traced to the father and mother both of whom harbored this disease.

The child's birth and past history disclosed nothing of moment. She had developed normally and had never been ill.

Upon admission, the child appeared well nourished, somewhat obese, and did not appear to be in pain or discomfort. A complete physical examination failed to disclose any abnormality aside from a copious purulent vaginal discharge, with highly inflamed vaginal mucosa and excoriation of the external genitalia. The smear revealed pus cells and gonococci in great abundance. Her hemoglobin was 85 per cent; red blood cells 3,800,000, white cells 8,400 with 72 per cent polymorphonuclears and 28 per cent lymphocytes.

Treatment by local diathermy having failed to bring about any improvement, it was decided to resort to heat therapy. Accordingly she was transferred to the inductotherm bed at 7:10 A.M., May 14, 1937. Her temperature at this time was 98.8°, pulse 112, and respirations 24.

At 8 A.M. her temperature had risen to 100.6° and continued to rise steadily at the rate of approximately 1° F. per fifteen minute interval, and at 9:45 the thermometer registered 106.6°; her pulse had steadily risen to 168 and respirations fluctuated from 24 to 32. Because of crying and restlessness she had received a hypodermic injection of sodium luminal gr. 4 at 9 A.M. This exerted only a moderately satisfactory calming effect. Short periods of sleep alternated with bouts of restlessness. Fifteen minute periods of observation up to 12:15 P.M. showed her fever to fluctuate between 106.2 and 106.8°; the pulse ranged from 162 to 168, and respirations remained at 32. The pulse was described as being of fair quality. From 12:30 P.M. to 3:30 P.M. her temperature range was 107 to 107.4°, pulse remained at 168 to 178 and respiration varied from 36 to 56. During this latter interval she slept but could be easily aroused for her sodium chloride solutions. She had received in the course of her fever session 1,000 c.c. 2 per cent salt solution and water. At 3:30 P.M. her treatment was terminated and she was transferred to the pediatric ward in a satisfactory condition which remained unchanged until 6 P.M. During this time the patient was asleep, her temperature taken at half hour periods registered 106.4 to 106.8° and her appearance occasioned no alarm.

At 6:30 P.M., she suddenly became very cyanotic, her respirations became rapid and irregular, circulatory collapse supervened, and her temperature registered 108°, and 108.6° a half hour later. Vigorous stimulation in the form of metrazol caffeine, etc., and oxygen inhalation were instituted. In addition, cold sponging, a cold pack and colonic flushing were ordered. As a result of these antipyretic measures her temperature began to drop and at 9:15 had reached 104°. The patient appeared less cyanotic, respirations had improved, and she was able to swallow.

The temperature continued to fall rather rapidly and reached 98° at 10:15 P.M. Thereupon the cold applications were discontinued but the temperature continued nevertheless to decrease and by 10:40 P.M. had dropped to 94°, and the patient's condition appeared most precarious. The pulse became imperceptible and the respirations exceedingly shallow. External heat, metrazol, adrenalin intracardially, failed to bring about any improvement and the patient expired at 12:07 A.M., May 15.

Permission for autopsy could not be obtained.

SUMMARY

A healthy robust child, two and one-half years of age, died shortly after the termination of the first hyperpyrexia treatment instituted for the control of specific urethritis.

Death, in all probability, was due to circulatory failure and exhaustion of the heat-regulating mechanism.

Treatment was carried out under expert supervision, and with scrupulous regard for all precautions usually observed in the application of this form of therapy.

This death constitutes, as far as could be learned from the available literature, the only one thus far recorded as having occurred in childhood as a result of induced hyperpyrexia.

A study of the literature discloses the fact that most of the deaths from induced hyperpyrexia have occurred in young healthy individuals.

The obvious conclusion is that no patient shall be subjected to this treatment unless made thoroughly aware of the very grave hazard involved.

The very serious question may properly be raised as to whether it is wise to recommend a treatment that may result in death, when the indication is an infection that is rarely serious, and which can satisfactorily be controlled by methods which experience has demonstrated to be entirely safe, though admittedly more time consuming.

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ACUTE HEMOLYTIC ANEMIA DEVELOPING DURING STREPTOCOCCUS SEPSIS

Report of a Case in Which Sulfanilamide was Given After the Anemia Had Developed

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ACUTE hemolytic anemia has been described by Lederer[1] who regarded it as an anemia of infectious origin. Parsons and Hawksley[2] write that there is no certain knowledge of the etiology, and state that like all other writers on this subject they have been unable to discover the infecting agent. They believe it possible that the same picture can be produced by more than one etiologic factor. In one case of their series a recurrence of hemolysis occurred coincidentally with an attack of pyelitis (*B. coli*) and recovery began as soon as the pyelitis was cured, but they do not know whether the two incidents were related. Harvey and Janeway[3] have recently reported on the development of acute hemolytic anemia during the administration of sulfanilamide. Their patients were being treated for streptococcic and meningococcic infections. They state that the clinical picture shows a striking resemblance to the cases of Lederer's anemia that were reviewed by O'Donoghue and Witts.[4] Harvey and Janeway could find only one instance of this type of acute hemolytic crisis in the records of the Johns Hopkins Hospital during recent years and none were observed during the course of a streptococcus sore throat. Whatever the action of sulfanilamide may be on the hematopoietic system, it has seemed that acute hemolytic anemia has been more frequently observed since the introduction of sulfanilamide therapy. The case to be reported here is of special interest in that acute hemolytic anemia developed during the course of a streptococcus infection before sulfanilamide was given.

CASE REPORT

J. A., male, aged twenty-three months, was admitted to the Milwaukee Children's Hospital on May 26, 1937, with the complaint of fever, restlessness, and swollen glands in the neck. He had had a mild head cold for a week, but was not ill, until the day before admission when he became feverish and restless. The glands on the left side of the neck were enlarged and the breathing was through the mouth. He had previously been admitted to the hospital on Dec. 17, 1936, at the age of eighteen months, for an acute upper respiratory infection and purulent otitis media. The blood count at that time showed white blood cells 10,000 of which 51 per cent were neutrophiles, 48 per cent lymphocytes, and

From the Milwaukee Children's Hospital.

1 per cent monocytes. The hemoglobin was 11 grams. The urine was normal and the Kline and Mantoux tests were negative.

On this admission the temperature was 103.5° F. The child was listless, but very irritable when disturbed. The mouth was held open and the respirations were noisy. The throat was full of mucus. The tonsils, pillars, and pharynx were acutely inflamed. There was bulging at the upper pole of the left tonsil and the swelling was soft and fluctuating. The left eardrum was red, but there was no bulging. There was marked cervical adenitis on the left side of the neck. The rest of the physical examination was negative. The diagnosis was acute tonsillitis with peritonsillar swelling on the left side and cervical adenitis.

The laboratory examinations showed the following: Blood: white blood cells 28,000, neutrophiles 78 per cent, lymphocytes 17 per cent, monocytes 4 per cent, plasma cells 1 per cent, hemoglobin 11 grams. Urine: albumin a trace, acetone plus, diacetic acid negative, sugar negative, sediment negative. Throat culture: mixed infection with streptococci present.

The peritonsillar swelling began to subside without incision, the temperature dropped and the child seemed better during the next two days. On May 29, 1937, three days after admission the temperature arose again to 103.8° F. The child seemed very ill. The skin was pale and there was slight jaundice. Emesis of food occurred. The spleen became palpable and the liver was enlarged. The throat, however, seemed much improved with less peritonsillar swelling, but the cervical adenitis was still marked. A blood culture taken on this date was later reported positive for hemolytic streptococci.

The blood count showed striking changes. The red blood cells were 2,000,000 and the hemoglobin 6.5 grams (color index 1.1). There was marked anisocytosis, poikilocytosis, and achromia. The white blood cells had increased to 34,700. The neutrophiles were 78 per cent of which 52 per cent were segmented, 12 per cent were nonsegmented, 2 per cent were metamyelocytes, and 2 per cent were myelocytes. The lymphocytes were 27 per cent and the monocytes 5 per cent. The icterus index was 30, and the van den Bergh showed a positive indirect reaction and a slight delayed positive direct reaction. The fragility test showed beginning hemolysis at 0.50 per cent saline and complete hemolysis at 0.34 per cent saline, while the control was 0.46 per cent for beginning and 0.32 per cent for complete hemolysis. The urine was positive for albumin, with red blood cells, white blood cells, and granular casts in the sediment.

Up to this time the patient had received no drug therapy, but since he had a streptococcus sepsis, sulfanilamide (prontylin) grains 5, three times a day was begun on May 30, 1937, and discontinued four days later on June 4, 1937. The patient received 60 grains during this time. We were not aware at that time of any contraindications to sulfanilamide therapy and believed that this was an ideal case to try the effect of the drug. It was discontinued after a second blood culture on June 3, 1937, showed no growth, the temperature had subsided, and the patient seemed much better. The sudden development of severe anemia on May 29, 1937, with evidence of hemolysis was treated by giving a blood transfusion (205 c.c.).

On June 1, 1937, the blood count showed red blood cells 1,400,000, hemoglobin 7.5 grams, white blood cells 41,100. The differential count was, segmented neutrophiles 17 per cent, nonsegmented neutrophiles 20 per cent, myelocytes 11 per cent, monocytes 3 per cent, lymphocytes 44 per cent, blast cells 5 per cent. There were eleven nucleated red blood cells seen in counting 100 white blood cells. The reticulocytes were 7.8 per cent. There was marked anisocytosis, poikilocytosis, and achromia.

TABLE I

BLOOD CHANGES DURING ILLNESS

	5/27/37	5/29/37	6/1/37	6/3/37	6/7/37	6/11/37	6/17/37	6/19/37	6/21/37	6/28/37
Leucocytes	28,000	34,700	41,100		21,400	12,800	22,400	9,200	8,600	9,400
Segmented neutrophiles (per cent)	77	52	17		42	38	45	51	39	7
Nonsegmented neutrophiles (per cent)	1	14	20		5	10	10	10	6	3
Myelocytes (per cent)		2	11				1	1		
Eosinophiles (per cent)					6	3	2	3	3	4
Monocytes (per cent)	4	5	3		3	12				
Lymphocytes (per cent)	17	27	44		44	41	42	35	52	86
Blast cells (per cent)	1		5			2				
Red blood cells in millions		2.00	1.40	2.00	3.90	3.30	2.90	2.05	2.90	4.20
Hemoglobin—grams	11.0	6.5	7.5	6.5	8.5	9.5	5.5	6.0	9.5	10.5
Color index		1.1	1.8	1.1	0.75	0.96	0.63	0.99	1.1	0.80
Nucleated red blood cells (per cent)			11							
Anisocytosis		Marked	Marked				Marked			Slight
Poikilocytosis		Marked	Marked				Marked			Slight
Achromia		Marked	Marked				Marked	Marked		Slight
Reticulocytes (per cent)			7.8	1.7	0.3	0.5	0.1	0.1		0.1
Blood platelets								162,000		
Additional procedures	T. 103.5° F. Peritonsillar swelling Cervical adenitis	Transfusion Blood culture positive for hemolytic streptococcus Icterus index 30 T. 103.8° F. Sulfanilamide started	Transfusion T. 100° F. Hemorrhagic nephritis Fragility test: patient 0.50-0.34; control 0.46-0.32	Transfusion Urobilinogen in urine positive Blood culture sterile Sulfanilamide discontinued 6/4/37		Transfusion on 6/9/37	Temperature normal	Transfusion on 6/18/37 Icterus index 6		

Another blood transfusion of 180 c.c. was given, and since the red blood cells were 2,000,000, and the hemoglobin 6.5 grams on June 3, 1937, a third transfusion of 190 c.c. was given. The reticulocytes had decreased to 1.7 per cent. The urine showed a mild hemorrhagic nephritic with albumin, red and white blood cells, and casts in the sediment.

The further course of the disease was marked by a gradual clinical improvement. The jaundice cleared rapidly and the spleen was no longer palpable on June 11, 1937. The anemia remained marked for some time and two more transfusions were given together with iron therapy and later liver and iron therapy. The nephritis persisted for some time and at the time of discharge on July 1, 1937, there were a few blood cells in the urine sediment, but no albumin or casts.

The patient was readmitted in good condition on Aug. 3, 1937, for the removal of tonsils and adenoids, and at the time of discharge on Aug. 6, 1937, the urine showed no albumin, red blood cells, or casts.

COMMENT

This case of acute hemolytic anemia would come under the classification of Lederer's anemia, except that the etiology here is presumably a streptococcus angina with streptococcus sepsis. The cases reported by Lederer were probably infectious, but no definite cause could be discovered. However there is no essential difference in the blood picture between this case and Lederer's cases. The acute hemolytic anemias which occur during the administration of sulfanilamide are likewise of the same type. Harvey and Janeway state that the hemolytic crisis produced by the use of phenylhydrazine resemble the acute hemolytic anemias during the administration of sulfanilamide. O'Donoghue and Witts write that the syndrome of the acute hemolytic anemia of Lederer resembles most closely infectious anemias such as Bartonella infections of man and animals. Whether one should call an acute hemolytic anemia of unknown etiology a case of Lederer's anemia and place all of these cases in a separate group is a question that cannot be answered until more studies have been made.

The increasing number of reports[5] on the toxic effects of sulfanilamide especially on the blood and skin, are of value in calling attention to the caution which should be exercised in using this drug, even though these undesirable reactions do not occur frequently.

It is of interest to speculate as to the effect of sulfanilamide in this case. Whether from the use of this drug or the blood transfusions or from natural causes, the streptococcus blood infection cleared up in a few days. The anemia, once the hemolytic crisis was over, proved quite resistant and five transfusions were given before the blood count approached normal, one month after the onset of the illness. It is impossible to state whether the use of sulfanilamide in this case prolonged or intensified the blood condition. It probably should not be used in a condition of this kind, although one could believe that the patient recovered because of its action in the clearing of the sepsis.

CONCLUSION

A child with a streptococcus throat infection developed an acute hemolytic anemia a few days after the onset of the illness. A positive blood culture for hemolytic streptococci was obtained. Sulfanilamide was then given. Recovery occurred in one month with five blood transfusions.

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425 E. Wisconsin Avenue

A SHEET BANDAGE FOR THE TREATMENT OF ECZEMATOUS CHILDREN

HERMANN VOLLMER, M.D.
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THE elimination of itching and the prevention of scratching are important considerations in the treatment of eczema. The tormented eczematous child frustrates again and again every therapeutic success by scratching, i.e., by mechanical irritation and destruction of epithelium in the diseased skin area. There are three ways to break this vicious cycle: (1) the local application of remedies which relieve the itching, (2) the calming of the nervous system by sedatives, and (3) mechanical measures that prevent scratching.

Fig. 1. Fig. 2. Fig. 3.

The available local remedies are unsatisfactory; they temporarily appease the itching, but do not eliminate it entirely. Sedatives alleviate the suffering to a great extent, but likewise cannot entirely prevent the itching. Therefore one cannot dispense with the common measures used for keeping the child from scratching, namely fastening the hands or extending the arms by cuffs or splints. These methods likewise are not very satisfactory. Fastening the hands occasionally causes venous congestion and strangulation. Extending the arms by

From the Pediatric Service of The Mount Sinai Hospital, Chief of Staff, Bela Schick, M.D.

splints requires bulky pads and bandages which cause the skin to overheat and perspire, and have an unfavorable influence on the eczema in case the skin of the arms is also involved. Moreover, the upper edges of the cuffs or splints offer the patient an opportunity to chafe the face. All these methods are regarded to be cruel fettering.

One has to consider that man changes his sleeping posture almost every fifteen minutes. If eczematous children are denied these physiologic changes of posture for days and weeks, central nervous disturbances may result. We have seen eczematous children restricted in their movements who were pathologically excited in spite of high doses of phenobarbital. After removing the bandages, these children frequently became calmer even when phenobarbital was discontinued.

Herein a method is described to wrap an eczematous child in a sheet so that changes in posture and movements of the arms remain possible —thus eliminating the tormenting feeling of being fettered—and yet scratching of body or face is entirely prevented.

As demonstrated in the figures, the child is placed in the middle of a quadrangular sheet so that the neck lies upon the upper edge of the sheet. The sheet is then folded from both sides over the shoulders and arms, drawn under the armpit, then around the back, and knotted above the chest (Figs. 1 and 2). Thus the arms in the sheet wrapping are allowed full play which can be regulated at will, but they cannot be lifted toward the chest or face. The lower edge of the sheet is finally drawn up between the legs and fastened with safety pins on both sides in the region of the shoulder, in order to avoid movement of the bandage (Fig. 3).

This sheet bandage is practical for hospital use as well as for private practice. It is hygienic because the sheet can be changed as frequently as necessary. It avoids overheating because it dispenses with bandages and pads, and can be applied on the undressed child in the summer time. The children although unable to scratch themselves do not feel disagreeable nor confined.

25 Central Park West

NETTING RESTRAINT OVER HOSPITAL CRIB

Safety Device

Jerome L. Kohn, M.D.
New York, N. Y.

VARIOUS devices are being used to prevent active young children from climbing out of, or falling from, hospital cribs. The most common device now in use is a canvas vest with attached tapes which tie to the side bars of the crib. Canvas strips tied from the ankles

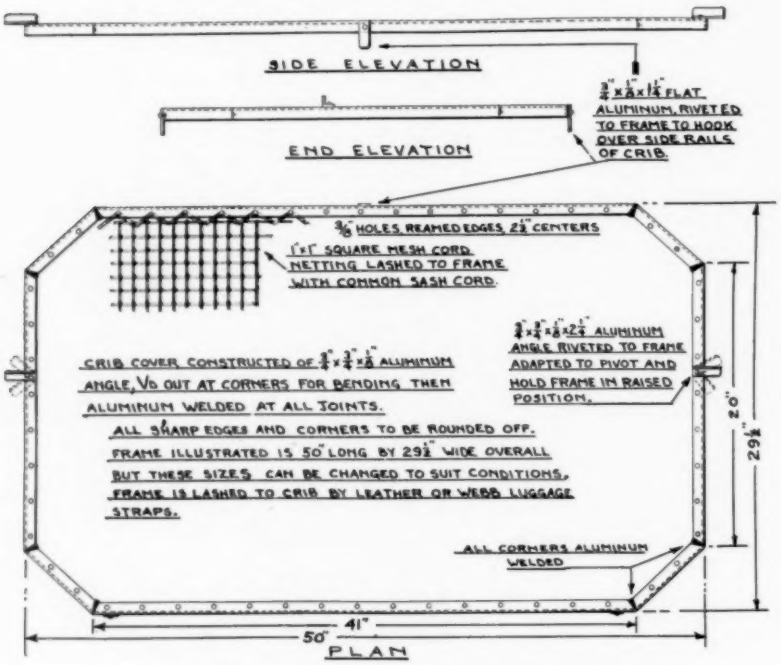
SIDE ELEVATION
END ELEVATION
¾"×¾"×1¼" FLAT ALUMINUM, RIVETED TO FRAME TO HOOK OVER SIDE RAILS OF CRIB.
⅜" HOLES REAMED EDGES 2½" CENTERS
1"×1" SQUARE MESH CORD NETTING LASHED TO FRAME WITH COMMON SASH CORD.
¾"×¾"×⅛"×2½" ALUMINUM ANGLE RIVETED TO FRAME ADAPTED TO PIVOT AND HOLD FRAME IN RAISED POSITION.
CRIB COVER CONSTRUCTED OF ¾"×¾"×⅛" ALUMINUM ANGLE, V6 OUT AT CORNERS FOR BENDING THEM ALUMINUM WELDED AT ALL JOINTS.
ALL SHARP EDGES AND CORNERS TO BE ROUNDED OFF.
FRAME ILLUSTRATED IS 50" LONG BY 29½" WIDE OVERALL BUT THESE SIZES CAN BE CHANGED TO SUIT CONDITIONS.
FRAME IS LASHED TO CRIB BY LEATHER OR WEBB LUGGAGE STRAPS.
ALL CORNERS ALUMINUM WELDED
20"
29½"
41"
50"
PLAN

Fig. 1.—Plan of netting restraint used over hospital cribs.

or wrists to the sides of the crib are also used. We felt that the above methods of restraint limited the child's movements too much and were frequently harmful physically and psychologically. We, therefore, suggested the following device.

For many years we had used a plain square mesh netting (1 inch by 1 inch tennis netting), which was lashed over the sides and ends of the crib with common sash cord. The child could sit up if desired and if

From The Pediatric Department of the Mount Sinai Hospital.

it attempted to stand, it could not possibly hurt itself. When the child required attention, however, the unfastening and relacing of the netting was an awkward, time-consuming process.

Fig. 2.

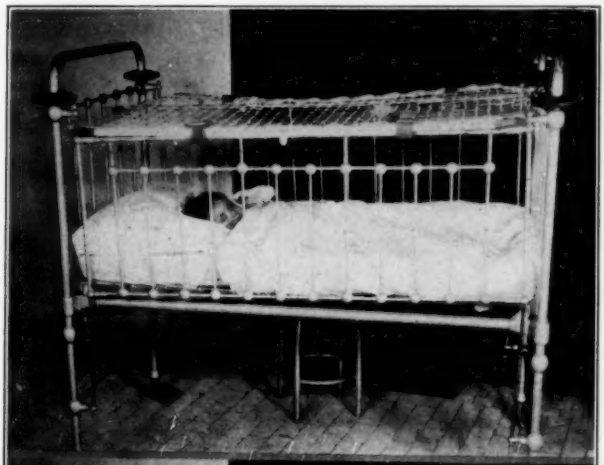

Fig. 3.

Fig. 2.—Crib with attached netting restraint.

Fig. 3.—Netting restraint in raised position while child is being tended. This illustrates the use of the aluminum strips adapted to pivot and hold the frame in a raised position.

Miss Mildred M. Sherwood, formerly head nurse of the infants' ward of the Pediatric Service at Mount Sinai Hospital and now nurse in charge of the Pediatric Service at Duke University Hospital, suggested that the netting be mounted on a wooden frame, fitted to the crib. The entire frame could then be lifted off the crib when necessary.

Recently, with the aid of Messrs. John B. Cubberly and Neil MacDonald, of the Engineering Department of the Mount Sinai Hospital, a light metal angle frame was devised (Figs. 1, 2, and 3). This frame has no sharp edges or corners. A piece of aluminum is riveted to the sides of the angle frame to hook over the side rail of the crib for greater security. Another strip of aluminum is riveted to each end of the frame, adapted to pivot and hold the frame in a raised position while the child is being tended. Rubber snubbers can be attached to the under surface of this frame to keep it from scratching the rails.

The frame is usually fastened to the side rails of the crib with web or leather luggage straps. There are two such straps on each side. When one side is raised, the straps on the opposite side act as hinges. These luggage straps have not proved entirely satisfactory especially in children over two and one-half years of age because occasionally such children are able to unfasten the straps. We have tried various devices to overcome this defect. An ordinary padlock with a chain shackle has proved to be satisfactory, and we are using such locks at the present time. Two padlocks are attached to one side of the crib and only one lock on the side which is usually lifted. All the locks on the ward can be unlocked by the same key. A key, attached to a large metal ring, is kept near the crib.

The advantages of this type of netting device are: (1) There is little or no restraint except on standing; (2) the child cannot harm himself; (3) the frame is ready for immediate use; (4) the netting can be easily sterilized, and the frame can be thoroughly washed; and (5) it is not necessary to remove the frame when tending the child.

50 West Ninety-Sixth Street

AN INTRAVENOUS NEEDLE HOLDER

ROBERT COHEN, M.D.
CHICAGO, ILL.

THIS instrument is introduced as a needle holder for intravenous infusions.

The present procedure for intravenous infusions at the Cook County Children's Hospital is the use of the Spivek[1] or the Hendon[2] technique (an intravenous cut down).

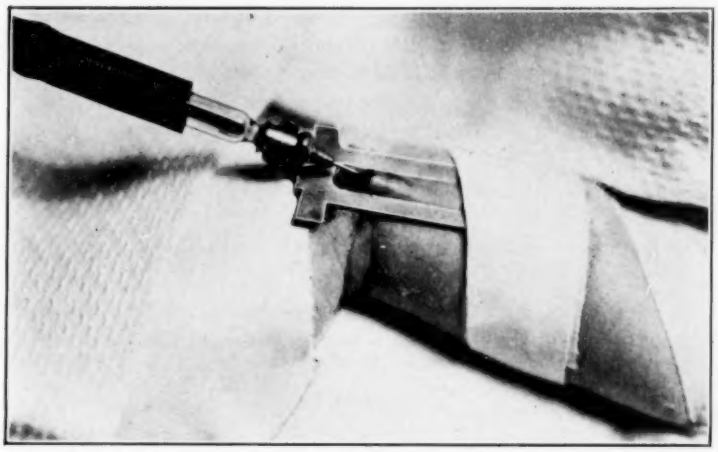

Fig. 1.

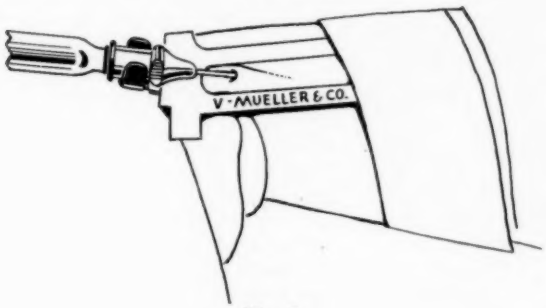

Fig. 2.

This new device facilitates correct angulation for needle and abolishes the gauze pledget build-up. In places such as the wrist or ankle vein where the hilt of the needle protrudes out beyond the skin, this instrument can fit the needle more securely than any known device.

From the Cook County Children's Hospital.

There need be no fear of movement causing dislodgement or perforation of the vein because the distance of the needle holder clip is constant and the skin attachment does not allow the extremity to move without the instrument always moving in the same parallel position.

The principle is a needle clip on a friction hinge attached to a U bar. After the needle or cannula is inserted into the vein, the U bar is slipped under the needle and moved forward until the clip is inserted on the hilt of the needle. There it is angulated to the proper degree desired. The front of the parallel bars is taped to the skin, and the base wings taped if desired.

Next, the adapter is connected with the needle, the stop-cock is released and the blood or the solution used is allowed to flow in. Whenever the operator desires to use the direct method of transfusion in place of the indirect method, all that is necessary is to insert the syringe instead of the rubber tubing with the adapter as previously described.

When patients are bathed or are to be moved to another room for roentgenograms, or other procedures, one merely inserts a stylet into the cannula and continues with his task without the fear that the needle will be dislodged.

This holder can be used equally effectively on the wrist, ankle, popliteal, or cubital spaces.

The pictures of this instrument illustrate the advantages set forth.

The models used were generously made by V. Mueller and Company, Chicago. Exhibited at Region III Meeting of the American Academy of Pediatrics, Oct. 14, 1937.

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American Academy of Pediatrics

Proceedings

SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK, N. Y., JUNE 3, 4, AND 5, 1937

Round Table Discussion on Vitamins

Chairman: Dr. Hugh Chaplin, New York City
Assistants: Dr. Mary Swartz Rose, New York City
Dr. Henry C. Sherman, New York City

Vitamins C and D

Hugh Chaplin, M.D.

Vitamin C, in its chemically pure form, is colorless crystalline hexuronic acid. It is synthesized in plants from a number of closely related pentose and hexose sugars. Some animals, such as the rat, chicken and dog, can synthesize vitamin C. Man, however, cannot do this and must depend for its supply on the food he eats. Chemically pure vitamin C has been called ascorbic acid, but at the suggestion of the American Medical Association it has become customary in the United States to refer to vitamin C as cevitamic acid.

For the purpose of accuracy and uniformity of dosage 1 international unit equals 0.05 mg. of pure crystalline cevitamic acid, or the amount contained in 0.1 c.c. of fresh lemon juice. It can be synthesized in the laboratory and is now prepared commercially.

Amounts present in food, tissues or excretions have been measured in many ways, one of the most recent of which is by titrating a fairly stable solution containing the vitamin with certain reducing dyes. Although decidedly useful such titration methods are as yet far from entirely satisfactory.

Citrous fruits are the richest food sources of vitamin C; tomato juice is a fairly rich source of the vitamin, whereas potato is a moderate one. Although cow's milk is generally a rather poor source, it regularly contains more vitamin C in the summer when cows are in pasture than when they are on the usual winter feed. Certain breeds, the Brown Swiss for instance, are said to have somewhat more vitamin C regularly than the Holstein breed. Also the amount of the vitamin is said to vary with the period of lactation. The same kinds of food are said to contain varying amounts of the vitamin depending on the type of soil in which they are grown.

In the human body vitamin C is present both as reduced and as reversibly oxidized cevitamic acid. The former has more vitamin C power. It is possible that the latter is made more effective by being converted back to the active reduced cevitamic acid by an enzyme in the blood.

The vitamin can be stored for a short time and up to a certain normal saturation level. Liver, adrenals, pituitary, and corpus luteum are especially rich in vitamin C. Blood and lean meat have the least of the vitamin. Two to four months of a vitamin C-free diet probably exhausts the complete normal storage in the adult, and six weeks in the infant. Normal adults excrete 15 to 20 mg. of cevitamic acid a day in the urine. After the body has reached its normal saturation with vitamin C it is excreted in the urine in proportion to its intake.

The functions of vitamin C in the human body are various. It is a special kind of reducing agent. When there is a deficiency, the intercellular cement substance between endothelial cells is not formed normally. This very naturally favors increased capillary fragility and results in frank hemorrhage. Deficiency of vitamin C interferes with normal tooth structure, with normal tissue repair, and permits of greater injury to tissues by such poisons as diphtheria toxin. The "cardboard flavor" which is sometimes noted in cow's milk is associated with a small amount of vitamin C and often in the presence of oxidation. During a deficiency of the vitamin there is a progressive decrease in the ability of the human body to dispose of absorbed sugar.

It must be remembered that, whereas additional vitamin C will correct all these particular symptoms, it also makes for a general condition of optimal health which cannot always be analyzed into all of its separate parts.

Vitamin C is, of course, water soluble. Chemically pure crystalline cevitamic acid is soluble in water. It is quite stable to ordinary heat and oxidation, whereas the vitamin in natural foods is the most unstable of all the known vitamins, being almost entirely destroyed by the heat of ordinary cooking, especially in the presence of oxygen. It is more easily destroyed if it is in solution and if it is alkaline in reaction. Copper acts as a metallic catalyst oxidizing and destroying vitamin C even in an acid media and even if only a very little copper is present.

A marked deficiency of vitamin C produces the symptoms of scurvy. A lesser degree of deficiency results in subclinical symptoms variously enumerated as follows: sallowness, loss of energy, fleeting pains in limbs, poor appetite, slow healing of wounds; or irritability, some retardation in growth, possible increased capillary fragility, and increased susceptibility to infections.

There is much individual variation in the amount of vitamin C needed. It has long been noted clinically that under apparently similar feeding conditions certain infants have developed scurvy much sooner than others. It may be due to differences in the rapidity with which vitamin C is absorbed, stored, and utilized. Also an individual, almost depleted of the vitamin, will temporarily require more than one who has been receiving an adequate supply all along. It has been estimated that 25 mg. a day of cevitamic acid will protect an infant from scurvy. Much more will be needed to cure a florid case of scurvy. It is probable that vitamin C is used up more rapidly than usual by such conditions as increased metabolism caused by hyperthyroidism, pregnancy, lactation, exhausting effort, acute infections, and possibly severe malnutrition. Apparently the minimum amount needed to prevent scurvy is only a fraction of the desired amount for optimal health.

So far as is known, it has never been possible to produce toxic symptoms by giving large doses of vitamin C.

There are a number of commercial preparations available of chemically pure crystalline cevitamic acid in tablet form. Each tablet contains 25 mg. or 500 international units.

Vitamin D in the chemically pure state is an alcohol called calciferol. It is fat soluble. Both in its pure form and in natural foods it is quite stable to both heat and oxidation. The U.S.P. and international units are the same, i.e., 1 unit = 1/40,000 mg. of calciferol.

Ergosterol is called provitamin D because, if this chemical substance is correctly irradiated with ultraviolet light and then taken into the human body, it accomplishes the same results as vitamin D itself, in fact it has become vitamin D. When irradiated, ergosterol is called viosterol.

There are many sources of vitamin D available for man: Of the natural foods, egg yolk contains a moderate amount. By far the richest source of the vitamin is the fish oils, i.e., of cod, halibut, percomorph, etc. Another natural source is the sunlight. Its rays are probably absorbed by the sebaceous secretions of the skin, as a result of which vitamin D is formed in the body.

Of the artificial sources available for man there is first of all the pure crystalline calciferol previously mentioned. There is also viosterol and the artificial ultraviolet rays produced by special lamps. There are also the artificially enriched foods, the most important of which is milk. This has been provided by three different processes: the first, by feeding irradiated yeast to cows. The milk of these animals has been provided with over 400 units per quart. The second method is to irradiate a thin film of milk just the correct amount. This method provides a quart of milk with about 200 units of vitamin D. The third method of enriching the vitamin D content of milk is to add a measured amount of vitamin D concentrate to milk. The effectiveness of these three methods is about the same according to our present knowledge. More study of this question is needed.

The action of vitamin D in the human body is to assist in the absorption and utilization of calcium and phosphorus from the food. It keeps the percentage of these two elements in the blood up to normal and so aids in normal bone formation and normal nervous tissue health. This action of vitamin D is assisted if the reaction of the intestinal tract is kept somewhat acid and if calcium and phosphorus are present in the most easily absorbable form and in a plentiful supply.

Vitamin D is stored to a considerable degree in the human body, especially in the liver. An increase in the storage in the mother's body ante partum increases the amount stored in the infant's body and enables the mother to secrete a greater amount in her milk. Therefore it is important for pregnant and lactating women. It also aids older children to maintain a condition of optimal health, one phase of which is healthy teeth.

The symptoms of a definite deficiency are those of rickets and tetany.

As is the case with vitamin C, there seems to be a considerable variation in the amount of vitamin D needed by different infants. Premature infants need larger doses proportionally than full-term infants. Rapidly growing children need more than those who grow slowly. There is also undoubtedly an individual variation, the reason for which is not always clear.

There is a preparation of the chemically pure calciferol, which is a solution of it in propylene glycol of a strength in which 1 c.c. equals 10,000 units, or 1 drop from the prescribed dropper equals 250 units. If this is administered in the day's supply of milk, it appears that only one-tenth the dose given in an oil or in other foods is necessary.

For full-term infants under one year of age adequate daily doses would be: 10 to 20 drops of viosterol; 2 drops of the propylene glycol solution of calciferol if administered in milk or 20 drops if in other foods; 10 to 20 drops of concentrated haliver oil and viosterol mixture; 3 teaspoons of pure cod-liver oil.

It is still not certain whether it is wiser to give a little of one of the above preparations when a vitamin D enriched milk is used for an infant's food. More study is required to settle this question.

Contrary to what is known at present about all the other vitamins, it is possible to obtain dangerous toxic symptoms by giving too large amounts of vitamin D. Prolonged use of excessive amounts will produce calcium deposits in blood vessels, the

kidney, and other organs of the body. There are however experiments in which as much as seventy-two times the amount ordinarily advised was used for long periods with a number of children without any undesirable results. Therefore, it is not likely that any reasonable amount of vitamin D will prove dangerous to human beings.

Vitamins A and B_1

Mary Swartz Rose, M.D.

Vitamin A, a derivative of carotene and cryptoxanthin (which are products of activity of the plant cell), recently isolated and crystallized is available to man in forms in which it occurs in plants, being convertible into the active vitamin A in the body by the action of the enzyme, carotenase. Its prominence in milk and eggs is highly suggestive of the importance which it has been found to have in the development and health of the young of many species, and the study of how such a normal nutrient functions has engaged the interest of physiologists and biochemists for the twenty-five years in which its existence has been known.

Vitamin A is known to be essential to growth, vision, and the integrity of the tissues of the tear glands, conjunctivae, and eyeballs, to fertility and lactation, and to the health of the urinary, respiratory, nervous, and hemopoietic systems, as well as to the normal condition of the skin, gums, and teeth. Many of the phenomena are due to keratinization of epithelial cells and more and more evidence accumulates that altered epithelial cells become the sites of bacterial activity. It cannot be predicted just where or when such a manifestation will occur. We seldom are concerned with a deficiency. We are perhaps most concerned with those who manifest no pathologic symptoms detectable by ordinary inspection, for the effects of vitamin A deficiency may be long delayed. Sherman and MacLeod have shown that an animal with every appearance of normality may fail to reproduce on a diet adequate in vitamin A for growth. They also show that along with the failure to reproduce successfully there also appear in early adult life an increased susceptibility to infection and a tendency to break down with lung disease at an age corresponding to that at which pulmonary tuberculosis so often develops in young men and women. This is especially significant in that the quantity of vitamin A in the lung tissues varies with the amount in the diet.

The capacity for storage of vitamin A is great. The value of the period of lactation (with a well-nourished mother) is well illustrated in the length of time it takes for manifestation of severe symptoms in a rat—a period corresponding often to three to five years in the life of a child! Thus the study of changes in susceptibility to infection in children with only a slight deprivation of the vitamin over a period of four to six months could scarcely be expected to lead to any definite conclusions.

Vitamin A has nothing to do with "immunity to common infections" including cold and influenza. But infections may interfere with utilization of vitamin A; also there may be deficient absorption due to gastrointestinal or hepatic disease. It has been demonstrated both clinically and experimentally that biliary fistulas induce vitamin A deficiency regardless of the amount of vitamin A in the diet. Hence patients suffering from vitamin A deficiency due to lack of bile should have bile salts orally, or the vitamin A should be given parenterally.

Clausen, who has given much attention to the question of nutrition and infection, points out that "the use of adequate diets before the onset of an infection is of more importance than the addition of vitamin A during an infection," and it might be added that, since infection interferes with vitamin A utilization, it is important to take care to restore body reserves afterwards. Many of our staple and popular foods are poor in vitamin A, e.g., meats, sugar, flour, potatoes. In infants the

routine use of two teaspoonfuls of cod-liver oil with normal milk intake without doubt insures ample vitamin A. Other foods of importance are eggs, green vegetables, and butter. Good allowances for this vitamin are shown in the following table.

Vitamin A: Suggested Allowances Per Day
(Sherman-Munsell Units)

Children at least 200 units per 100 cal.	
Children under 5 yr.	3000-4000 units
Children 5-10 yr.	4000-6000 units
Children 10-16 yr.	6000-8000 units
Adults at least 100 units per 100 cal.	
For freedom from colds	5000 units up
For pregnancy and lactation	5000 units up

Vitamin B_1.—Changes in the food customs of people have sometimes produced surprising results, and well-meant social aims led to nutritional disaster. Thus on the island of Naura, in Polynesia, to prevent drunkenness, the League of Nations stepped in and prevented the use of an alcoholic beverage prepared from yeast. The result was that inebriety disappeared, but beriberi broke out. Similarly, when American army officers sought to improve the fare in Bilibid prison in Manila after the Spanish-American War, they thought it proper to furnish the prisoners a better grade of rice—fine plump white rice—instead of the low-grade brownish rice which had been in use. This improvement was followed in a few months by an outbreak of beriberi. At first they thought it must be due to an infection, but finally it was realized that the diet might be at fault, and a change back to the darker rice and other improvements in the sources of vitamin B_1 cured the prisoners.

The long search for the pure substance which could produce such striking results in so short a time was to last for twenty-five years, until synthesized by Williams in 1936 and now named thiamin by him.

Different in chemical structure from vitamin A, vitamin B_1 is likewise different in its functions. Whereas structural changes in epithelial cells are the outstanding effect of deprivation of vitamin A, the changes due to lack of vitamin B_1 are so characteristically functional and so diversified that there is no objective test yet for mild states of vitamin B_1 deficiency.

Experimentally, the first effect of withholding the vitamin, after an interval to allow for exhaustion of body reserves, is retardation of growth, almost if not entirely simultaneous with loss of appetite. Because of the failure to eat, the young animal soon dies of inanition. By administration of vitamin B_1 when the animal is in a state of collapse, it is usually possible to restore appetite within a few hours after which the animal begins to consume food to the limit of its capacity and to grow at an accelerated rate until normal weight is attained, and then no symptoms of the previous shortage are apparent.

If the animal is only partially deprived of vitamin B_1 so that sufficient food is eaten to maintain weight or to induce slow growth, there will be time for the development of other symptoms, particularly polyneuritis. Although the manifestations are peripheral, the fundamental difficulty is in the central nervous system, the acute symptoms having been found by Peters to be due to accumulation of lactic acid. The chief sites of disturbance appear to be Dieter's nucleus, the chief vestibular nucleus, the nucleus of Bechterew—all concerned with the control of muscles for equilibration—and the nucleus solitarius concerned with the transmission of gustatory impulses from the tongue. Acute symptoms in pigeons have been cured in one hour by injections under the skull. Vitamin B_1 appears to be a catalyst for the conversion of lactic acid to pyruvic acid and the further oxidation of pyruvic acid. Sherman

and Elvehjem have studied the respiration of the vitamin B_1 deficient cerebrum in pyruvate solution and found the oxygen uptake seriously impaired, but the addition of small amounts of vitamin B_1 caused increased oxygen uptake and increased rate of removal of pyruvate.

Partial deprivation also gives opportunity to study the effects on the alimentary tract. McCarrison has repeatedly called attention to the common occurrence of alimentary disturbances in vitamin B_1 deficiency. He showed changes in tonus of the stomach and intestines of monkeys. Similar changes in the human alimentary tract were described by Fletcher. Cowgill has measured gastric atony in the dog by means of a balloon introduced into the stomach through a gastric fistula, and Sparks and Collins have made fluoroscopic examination of rat colons given an enema of sodium iodide solution. After two to three months of vitamin B_1 shortage there was great increase in colon volume. Drummond commenting on a long-time study of vitamin B_1 deficiency in rats says, "Our observations fully support the conclusions of McCarrison regarding high incidence of disorders of the alimentary tract." Several observers have reported observation of gastric ulcers (Dalldorf, Sure, Thatcher).

The influence of vitamin B_1 on growth is the resultant of several or perhaps many factors. Not only improved appetite and digestion, but better growth per unit of food eaten has been repeatedly observed. In the case of babies, Daniels and Byfield showed long ago that increased gain in weight followed the addition of wheat germ extract to a standard formula, or when the amount of orange juice was increased to three times that necessary to prevent scurvy.

Hoobler, Dennett, Bloxom, and others have convincingly shown the better growth and increased well-being of babies given liberal vitamin B_1, and Morgan and Barry and Tisdall and Sommerfelt have shown the same for older children. Milk is not sufficiently rich in vitamin B_1 to serve as the sole source in a child's diet. Wheat germ extract and yeast extract seem the most practical supplements for infants because of their solubility and high concentration of the vitamin.

For older children cereals, fruit, and vegetables along with a liberal milk intake will give a sufficient supply if chosen with regard to their vitamin B_1 content. The loss of the vitamin in vegetables in cooking may be high, even when the cooking water is not discarded, and the high temperatures to which whole grain cereal preparations are subjected may greatly reduce their vitamin B_1 content.

It is much easier to get a diet rich in vitamin A and vitamin C than one rich in vitamin B_1. The use of cereals with added germ is worth fostering and there is promise of a white bread reinforced with wheat germ in the near future.

The vitamin B_1 requirement is related to size, rate of growth, and total energy expenditure. Cowgill showed that speeding up combustion by administration of thyroxin increased the speed with which signs of vitamin B_1 deficiency appeared in dogs. It has also been shown that high doses of vitamin B_1 will enable hyperthyroid individuals to maintain their weight. The increased metabolism of fever likewise increases the vitamin B_1 requirement.

Many factors influence the effect of a given amount of the vitamin. It is not possible yet to make any test of individual differences except to give more liberal vitamin B_1 and see whether improvement results, no other change being made at the same time. A surprising number of people find digestion improved, and others note improved appetite and general well-being. The therapeutic response is at present the main diagnostic test of vitamin B_1 deficiency. Mild deficiency of vitamin B_1 can be the cause of vague pains and subacute indigestion, which cause restless sleep and generally constipation and poor appetite.

Suggested Allowances for Vitamin B_1 Per Day
(Sherman-Chase Units)

Under 1 yr.	200-300 units
2-5 yr.	300-600 units
Above 5 yr.	10-20 units per 100 cal.
Adult man	300 units
Pregnancy	400-600 units
Lactation	600 units up
Therapeutic treatment	4000 units

Heat-Stable Factors of the Vitamin B Complex

H. C. Sherman, M.D.

Vitamins A and B_1 (already discussed by Professor Rose) and vitamins C and D (already discussed by Dr. Chaplin) are, so far as I know, the only ones which are explicitly related to *specific clinical* pediatric conditions. But *at least two* of the relatively heat-stable substances of the vitamin B complex—vitamins G and H; *or* two parts of "the vitamin B_2 complex"—are now recognized as essential for the growth of the young, and for health at all ages, of mammalian species generally, doubtless including the human. Of these substances, one has been chemically identified and synthesized and is now known as lactoflavin or riboflavin. (These two terms are synonymous in present-day literature: the former having been more used hitherto; the latter being now recommended by the Council of Pharmacy and Chemistry of the American Medical Association, by the American Society of Biological Chemists, and by the American Institute of Nutrition.) Besides this, there is another substance, not yet chemically identified, but commonly designated as vitamin B_6. Whether the substance studied by Booher as vitamin H is or is not the same as vitamin B_6, and whether or not there is any *one* substance which holds the same relation to pellagra which vitamin B_1 does to beriberi and vitamin C does to scurvy, are still open questions.

What have been called units of vitamin G value in foods and nutrition are now interpreted as units of lactoflavin or riboflavin value. Rose and Stiebeling's minimum dietary standards for this factor in normal human nutrition are as follows:

Rose and Stiebeling Minimums for Riboflavin

*Dr. M. S. Rose**

For children up to 10 years of age: at least 400 units per day in all cases; 20 units per 100 Calories if more than 2000 Calories per day are consumed.

For adults: 20 units per 100 Calories.

Dr. H. K. Stiebeling†

For child under 4 years of age	450 units
For boy 4-6; girl 4-7	450 units
For boy 7-10; girl 8-13	540 units
For older child; adult	600 units
Per capita of the population	570 units

Recent tabulations of quantitative measurements of such values in a considerable number of foods, and of semiquantitative estimates for a still larger number, are

*Laboratory Handbook for Dietetics, ed. 4, 1937.

†Publications of the United States Department of Agriculture; and personal communication of April, 1937.

(One quart of milk = 600 ± 30 units, average of 13 findings in ten independent investigations.)

included in the fourth edition (1937) of Rose's *Laboratory Handbook for Dietetics*, and in the fifth edition (1937) of Sherman's *Chemistry of Food and Nutrition*.

Riboflavin combines with phosphoric acid and protein to form the so-called "Warburg's yellow enzyme" or "tissue respiratory enzyme" and may function in other ways also. While the details of its functioning are still under investigation, feeding experiments with different levels of enrichment of the dietary with riboflavin are indicating that increasing liberality of intake continues to promote growth and vitality to levels much above those of minimal adequacy or strictly demonstrable need.

The Problem of Optimal Rapidity of Growth

The laboratory findings just noted and both clinical and laboratory data on the relations of vitamin B_1 to appetite and growth combine to reawaken interest in the problem whether increased rapidity of apparently normal growth is practically always to be taken as a sign of present and prospective nutritional well-being or whether there is danger of unduly forced growth in any appreciable proportion of infants and children under present-day conditions. In certain of the laboratory animal experiments of McCay and Maynard at Cornell it appeared that longevity was favored by moderate restriction of early growth; while in the experiments of Sherman and Campbell at Columbia dietary adjustment has resulted both in more rapid growth and in longer life. There is no necessary contradiction between the Cornell and the Columbia findings because their dietary starting-points were so different: the Cornell diet was extremely rich in protein and vitamins, whereas the initial Columbia dietary was of about minimal adequacy, representative of the food supplies upon which the larger proportion of the people are for economic reasons now subsisting. So long and so far as such a food supply is the actual starting-point of our efforts to improve human nutrition, the taking of a larger proportion of the needed calories in the form of such "protective" foods as fruits, vegetables, and milk, promises not only to expedite growth and development but also (and in the same individuals) to enhance the norm of adult vitality and length of life.

DISCUSSION

DR. J. V. GREENEBAUM (CINCINNATI, OHIO).—What object has Dr. Rose in giving vitamin B as a concentrate?

DR. ROSE.—In terms of ordinary daily life rather than in prescription, it seems that we would be more successful in having the vitamins associated with food. The people might not continue to take extra vitamins for a long time otherwise.

CHAIRMAN CHAPLIN.—In view of the fact that occasionally milk is not well taken, it is good that we have other sources of vitamins.

DR. F. H. VON HOFE (EAST ORANGE, N. J.).—Does Dr. Rose believe that vitamin A acts against colds by aiding the epithelium?

DR. ROSE.—A vitamin is not anti anything. But those who have followed the course of colds as I have know that the recovery has been faster when the vitamin A intake was high, assuming an adequate general diet.

DR. VON HOFE.—Specifically are you justified in telling a mother that an increased intake of vitamin A will prevent colds?

DR. ROSE.—My ability to cope with colds seems to be improved by adding to the vitamin A intake.

DR. VON HOFE.—Should vitamin A and vitamin B be added to the diet of pregnant women?

DR. ROSE.—The diet is generally low in vitamin B. Since it is relatively high in vitamins A and C, not only pregnant women, but those who with advancing age get stouter, need extra amounts of vitamin B. We can get wheat germ at 5 cents per pound, but the marketing is still a difficult problem.

DR. HAROLD C. STUART (BOSTON, MASS.).—The pediatrician would like to have a simple objective method of deciding whether a child's blood showed deficiency of one or another vitamin.

DR. SHERMAN.—I believe this is a reasonable hope, but the workers in this field are not yet ready. Theoretically it is a sound ambition but will probably take years to accomplish. In the meantime more use should be made of the study of muscle tone. Our laboratory custodians can feel the flabbiness before any specific tests give positive results. Careful clinical experience may be ahead of laboratory tests on these points.

It makes me squirm to hear any general statement about the vitamins. Each vitamin should be studied independently. We need lifetime experiments with all vitamins.

DR. J. W. HOLMES (PHILADELPHIA, PA.).—We observed a wide variation of vitamin C as it occurs in canned foods. Is this due to the processing or in the tomatoes per se? We studied a large variety of tomatoes from North Carolina for their vitamin content. Apparently some varieties contained more vitamin C than others. We now want to test the various species of tomato in Massachusetts and also want to study the vitamin C content of the same species of tomato grown with different fertilizers and under different conditions.

DR. W. WESTON (COLUMBIA, S. C.).— Are there any untoward effects depending on the material used? Mellanby showed the decalcification effect of cereals.

DR. ROSE.—By reading their papers you will note that the diets used were not constant, e.g., olive oil was used instead of cod liver oil in the diets of those animals in which decalcification occurred. Subsequent work in Wisconsin and elsewhere has not borne out Mellanby's results.

DR. J. I. LINDE (NEW HAVEN, CONN.).—With the use of vitamin D by the laity is it important for us to know of toxic symptoms of vitamin D?

Several years ago when irradiated evaporated milk was first used, some of us noticed that some children developed colic or loose stools. Are diarrhea and colic symptoms of excess of vitamin D?

CHAIRMAN CHAPLIN.—Excessive vitamin D is shown by x-ray evidence of excess of calcification. The early symptoms I do not know. I do not know whether the irradiation might not have caused changes which led to colic or diarrhea.

Summary of Talk on Vitamins

Marietta Eichelberger, Ph.D.

In no instance have we been able to find that the reports of diarrhea and regurgitation from feeding irradiated evaporated milk have been based on other than impressions and hearsay. In fact, data from controlled experiments indicate that irradiated evaporated milk has no connection with such upsets.

When this rumor was first circulated several years ago, we wrote to Dr. Jeans, of Iowa, Dr. Stokes, of Philadelphia, and Dr. Tisdall, of Toronto, all of whom, as you may know, independently were carrying on controlled studies with well babies on

both irradiated evaporated milk and nonirradiated evaporated milk. Some of these studies were undertaken under in-patient and others under out-patient conditions. Dr. Jeans reported that he had observed no diarrhea in his babies, all of whom were hospitalized. Tisdall and Drake reported studies on 130 babies who were closely observed under home conditions with no case of diarrhea.

Dr. May, of Detroit, in an out-patient study of the antirachitic properties of irradiated evaporated milk with premature, weakling, and full-term babies found no difference as to stools or regurgitation between babies on irradiated evaporated milk and those on nonirradiated evaporated milk.

This subject was also discussed with Dr. Barnes and Dr. Brown who collaborated with Dr. Eliot, of the Children's Bureau, in the recent comprehensive study in Detroit. Dr. Barnes stated that the babies fed irradiated evaporated milk showed no unusual looseness of stools. In fact, it was his opinion that the tendencies among their babies were toward fewer stools.

Dr. Stokes has made observations first on 24 negro male infants, and later on 24 white male infants under in-patient conditions. The following year Dr. Stokes and Dr. Rapoport kept accurate records of all stools of 113 babies under home conditions on irradiated evaporated milk, which was the sole antirachitic agent. In a paper soon to be published these investigators are reporting their results. Throughout this study these babies had normal stools and no unusual regurgitation.

PROF. HANS ARON (BRESLAU, GERMANY).—The problem of accelerated growth in infants has been discussed in Germany because of increase in length of children of both the socially well to do and the poorer classes.

Children attending high schools are taller. What is the cause of accelerated growth which seems to be unquestionably combined with shortening of the time required for development? Menstruation occurs from one to two years earlier. Carpal centers appear earlier. Some German authors claim, first, that adolescence appears too early and, second, that it brings the period of fertility too early at a time difficult to cope with life. What is the cause of this more rapid development? It seemed to have occurred even when there was a shortage of food. It is of course a question of quality. Even with a diminished intake of protein a diet rich in the vitamins may cause accelerated growth. The heliogenic theory is that by greater exposure to the sun, growth is promoted. I do not believe in this theory. The ability to have greater amounts of vitamin even in winter and even by the poorer classes is probably responsible. Thus, according to the highly interesting experiments of Dr. Sherman, the cause of this accelerated growth is probably due to increased vitamins. Is this desirable? As a pediatrician primarily I am of the opinion that it may be necessary to reduce the intake of the amounts of vitamins.

DR. I. A. ABT (CHICAGO, ILL.).—Dr. Sherman asks whether it is good or bad that growth should be hastened; my experience is that, if you offer a right type of food and the correct amount, the baby will take what he needs.

All babies do not utilize vitamins in the same way. There may be a digestive, a hormonal, or an endocrine deficiency which influences these things. We should not isolate our thoughts to vitamins. We are not of the same architectural plan. We must not narrow our veins to vitamins alone.

SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK, N. Y., JUNE 3, 4, AND 5, 1937

Round Table Discussion on Gonococcal Vaginitis

Chairman: Dr. Richard W. TeLinde, Baltimore, Md.

CHAIRMAN TELINDE.—Three years ago Dr. James Brawner and I started working on the treatment of gonococcal vaginitis in children with the estrogenic hormone. Amniotin was used in various forms. This work followed the lead of Robert Lewis, of Yale University, who had treated and cured eight patients by hypodermic injections. Two cases had recurred. We attempted unsuccessfully to treat a series of patients by oral administration and hypodermic injections of amniotin in ethylene glycol solution. Another series were treated with hypodermic injections of amniotin in oil. In these, 72 per cent of the patients recovered. We then attempted to treat another series with 75 rat unit suppositories. All of these patients were cured. After a year's work, 35 cases in which children were treated with amniotin were reported, all being well at the time of the report.

Since then a total of over 140 children have been treated successfully. A recent follow-up of the first 100 patients treated showed 98 of them well after a period of from three months to two and one-half years after cessation of treatment. The two recurrences or reinfections were noted six and seven months respectively after treatment had been terminated. The patients were given another course of treatment and promptly became well.

No harmful effects from the therapy were noted either during the treatment or at the time of the check up. One child treated has started to menstruate at the age of 13 years. The histologic change in the vaginal mucosa to the adult type, which regularly occurred as a result of the treatment, was shown by biopsies to be transient.

The treatment as carried out today is the insertion of a 1,000 international unit (125 rat units) suppository into the child's vagina at bedtime. No other remedial measure is employed except ordinary cleanliness. The average time required for the profuse shedding of vaginal epithelium was thirteen days. This indicates the full action of the estrogenic hormone. The average time for the first permanently negative smear was seventeen days. Treatment was continued for two weeks after this, making the duration of the total average course of treatment about one month.

Reports in the literature depreciating and condemning the use of hormones in vaginitis were based on treatment with preparations that were not as strong or as effective as present-day products.

Objections have been raised against the use of hormones because the infection is urethral in type. I have found no evidence of gonococcal infection in the urethra in these cases. If it were present, the same epithelial changes should occur in the urethra as in the vagina. We should explain to the mothers that the discharge generally becomes more severe after a few weeks of treatment and is an indication of the shedding of the vaginal mucosa. Such a discharge is generally free from gonococci.

DR. I. PALMIERI (BROOKLYN, NEW YORK).—Can you split the suppositories and use part of one per treatment?

CHAIRMAN TELINDE.—Yes. Good results can probably be obtained with a smaller dosage than we have been using (1,000 international units per suppository

every twenty-four hours). We do know that results from the use of 800 international units have been as satisfactory as those from larger doses.

I must admit that this method of treatment is very expensive at present. However, when the duration under other forms of treatment and the expense of frequent office visits under the old regime are considered, the comparison is not so unfavorable.

DR. PALMIERI.—Have you noted any change in facial features of the treated children, resembling the facies of pregnant women?

CHAIRMAN TELINDE.—No.

DR. A. C. SILVERMAN (SYRACUSE, N. Y.).—What do you mean by "theelin reaction"?

CHAIRMAN TELINDE.—By "theelin or amniotin reaction" I mean the appearance of large quantities of epithelial cells in the vaginal washings, with the disappearance of the pus. In most cases this appears about two weeks after the beginning of daily treatments. In an occasional case, however, a longer time is required.

DR. JAMES W. BRITTON (ANNISTON, ALA.).—Do you find any rectal involvement in this type of infection?

CHAIRMAN TELINDE.—I have not found rectal involvement in any of my cases. I know there are those who talk about its occurrence, but I feel that many cases are misinterpreted. I think it is only natural that positive smears should be obtained from the anus and a little way into the rectum when the pus is constantly draining over this area. I have never seen any evidence of proctitis in any of the children under my care.

DR. L. E. GOLDBERG (NEWARK, N. J.).—Have you had patients who complained of abdominal pain which was relieved after a profuse vaginal discharge, giving the impression of a blockage?

CHAIRMAN TELINDE.—Where did you believe the blockage was? In the vagina?

DR. GOLDBERG.—Yes.

CHAIRMAN TELINDE.—In those cases I would not hesitate to dilate or slit the hymen to secure better drainage.

DR. J. L. REICHERT (CHICAGO, ILL.).—In a controlled series of cases we found that, while 80 per cent of the patients in the cases diagnosed as gonorrheal vaginitis by smear showed negative cultures for gonococcus, about 10 per cent were negative by smear and 20 per cent of those suspicious by smear gave positive cultures. In other words, the use of both cultures and smears yields a more accurate diagnosis of gonorrhea than either method alone.

We have found that exacerbations as distinct from reinfections can occur as late as nine months after apparent cure. The usual criteria of cure are far from adequate. In addition to repeated consecutive negative smears and cultures, the cervix must be free from evidence of inflammation before a cure can be presumed.

An adequate theelin reaction in the introitus, vagina, and cervix can be produced with a third of the intramuscular dose of theelin, if the hormone is given intravaginally in the form of suppositories. While theelin apparently cures more patients in a shorter time than does local treatment, we found that the incidence of recurrence in the group of patients treated by theelin was more than five times as great as in the group given local treatment. The use of local remedies in cases recurring

after treatment with theelin was by far the most uniformly successful therapeutic method for these patients. Two per cent protargol in tragacanth jelly was the most effective of the five local medicaments which were used by us.

DR. H. P. WRIGHT (MONTREAL, QUE.).—Were cultures taken from the anterior or posterior fornix?

DR. REICHERT.—They were taken from all over. Most of the positive cultures were obtained from the cervical surface of the vagina.

DR. PALMIERI.—What is the effect of the suppositories on trichomonas vaginitis?

CHAIRMAN TELINDE.—I have not seen the occurrence of trichomonas vaginitis in children. However, since it does occur in adult women, I doubt if the treatment would be of any benefit in children.

DR. GOLDBERG.—Have you used the suppositories in nonspecific infections? My results have been very poor when the estrogenic substance was given by mouth and hypodermically.

CHAIRMAN TELINDE.—My experience with nonspecific infections has been somewhat limited. I have had about one-half dozen cases in private practice and have treated them with amniotin suppositories, with good results. I have noticed, however, that there is a greater tendency for slight irritation to occur and perhaps for a slight serous discharge to persist than in the gonococcal cases, in which the cure seems to be a little more clear-cut.

DR. L. BARASH (NEW YORK CITY).—Have you used Corbus-Ferry gonococcus filtrate in any cases of gonorrheal vaginitis?

CHAIRMAN TELINDE.—I have had no experience with this preparation.

DR. GOLDBERG.—We have been treating with this filtrate a series of patients who have gonorrheal vaginitis at the Essex County Hospital for Contagious Diseases, for a period of about a year. I am a little reluctant to report on its value, as we have not as yet observed these patients over a long enough period following their discharge from the hospital as cured. I expect to report on our results in about four or five months.

DR. SILVERMAN.—Have you used sulphanilamide in these infections?

CHAIRMAN TELINDE.—I have not used this preparation. But Dr. Perrin Long, who has been much interested in its use, treated a few patients suffering from gonococcal vaginitis with this drug without success. He is very enthusiastic about the drug, and, if he admits no success, I am sure that such is the case.

DR. J. G. KRAMER (AKRON, OHIO).—I have under my care four patients with vaginitis, showing a profuse thick yellowish discharge. This discharge contains no pus cells but is composed almost entirely of epithelial cells. No parasites or offending organisms could be found. Nor has the condition responded to chemotherapy.

CHAIRMAN TELINDE.—I have not seen this condition in children but find it in adult females. I call it an "exfoliative vaginitis" and would suggest using suppositories.

L. E. GOLDBERG,
Newark, N. J.

JAS. G. KRAMER,
Akron, Ohio.

SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK, N. Y., JUNE 3, 4, AND 5, 1937

Panel Discussion on the Present Status of Active Immunization Against Whooping Cough

Chairman: Dr. Rustin McIntosh, New York, N. Y.
Assistants: Dr. Ralph S. Muckenfuss, New York, N. Y.
Dr. Minnola Stallings, San Francisco, Calif.
Dr. James A. Doull, Cleveland, Ohio

CHAIRMAN McINTOSH.—I wish to express my appreciation in being invited to be chairman of this panel. My own ignorance in this field is colossal. I have no first-hand information whatever, so I shall proceed at once. The list of speakers is somewhat altered. Dr. Shibley, unfortunately, is unable to be present, but his colleague, Dr. Doull, will speak instead. Obviously in a subject of this kind, where the interpretation of results is so extraordinarily difficult, we need to have a wide survey. With that point in mind, we have invited a speaker from the west coast, one from the middle states, and one from the east coast.

I should like to take the liberty of asking Dr. Stallings a few questions in connection with points not quite clear in my mind. Would she explain the difference between the Sauer vaccine, the Cutter vaccine, and the Krueger vaccine?

DR. STALLINGS.—The Sauer vaccine is a suspension of whole killed *Hemophilus pertussis*, while the (Krueger) pertussis U.B.A. is a filtrate of a suspension of the ground organisms. Phenol is the chemical agent used to kill the organisms in the Sauer preparations. In preparing the Krueger antigen no chemical or heat is used; the organisms are ground so that denaturation does not take place.

The Sauer vaccine is prepared by three biological laboratories: Eli Lilly and Company, Parke, Davis and Company, and Cutter Laboratory. The (Krueger) pertussis U.B.A. is prepared by Eli Lilly and Co., exclusively.

CHAIRMAN McINTOSH.—From the data assembled, have you any reason to feel that any one of these preparations is superior?

DR. STALLINGS.—Practically all the immunization was done with the Sauer preparations. Only one questionnaire gave information about using the Krueger antigen.

In 1933, following the preliminary report on treatment of pertussis with an undenatured antigen (U.B.A.), one pediatrician gave seventy-three children injections of the pertussis U.B.A. for immunization. He reports that, so far as he knows, only three have developed the disease. However, he does not know the number of contacts in this group.

CHAIRMAN McINTOSH.—What is the basis for the statement that from 75 to 80 per cent of susceptible children contract the disease?

DR. STALLINGS.—I am only quoting figures compiled by other workers. This refers to intimate contact. Kendrick's observation was that 76.5 per cent of a group of unimmunized children developed the disease after intimate contact.

CHAIRMAN McINTOSH.—It is obvious that there is a very great public demand for an effort to protect against whooping cough. I should not say for protection but for an effort to be made, and the wide distribution of this demand has been shown.

The difficulties in control of experimental work and the difficulties of interpretation are only too obvious; and with all due recognition of the handicap under which Dr. Stallings has worked in tabulating the results of her questionnaires, I think we must feel that studies made by individuals without strict control and without accurate information about contacts and careful computation of results are bound to be taken with a grain of salt and that, if we are to draw rigid conclusions, we must have rigidly planned experiments.

The natural transmission of pertussis is notoriously capricious, and I think it follows that adequate studies of this question of prophylaxis are perhaps out of the range of the individual and must be carried out by large clinics, public health departments, or other large groups who can plan the kind of experiment where the control is adequate.

That sounds a little pessimistic, but, to review the gains made in the last few years, I think this much is clear: we recognize that the antigen we now use is qualitatively better than the antigen available only a few years ago. Ten years ago, perhaps, the difference between the phases of the organism used in making the vaccine was not appreciated, and now it is agreed that, by using Phase 1 exclusively, we gain an improved quality of the vaccine.

There is still disagreement and lack of unanimity as to whether washing the antigen is deleterious, and there is no entire agreement as to the best method of sterilization to preserve the antigenic properties.

Another significant point is the quantity of vaccine necessary. Ten years ago or so the total dosages used in our exploratory efforts at whooping cough vaccination were of the order of three to five billion organisms. Now we know that we must get closer to the figure of eighty billion that Sauer advocates as the minimum necessary for effective vaccination.

It is impossible at the present time, and probably will be for a long period, to be certain how soon after the completion of vaccination the immunization can be regarded as effective. That perhaps is the last question that will be answered by the experiments that are being carried out; I think other questions will be answered sooner. We shall get a better idea as to how effective vaccination is in modifying the course of the disease, provided it is contracted after vaccination, and we shall get a much clearer idea of whether we can or cannot achieve complete protection.

I think it is obvious, too, in working with a disease like whooping cough, that we can scarcely demand absolute values. That is, to demand absolute protection is not being fair; so it is only reasonable on our part to be willing to accept partial success as a step in the right direction.

In conversation with physicians who have used the vaccine, I encounter at times a certain amount of opposition or discouragement on their part because a patient who had been given a full course of vaccine developed an attack of whooping cough four or six months later, and they sometimes think they should give it up entirely.

I do not feel that way myself. I think even partial success justifies further work. It seems pretty clear from the evidence presented, both the evidence published in the literature and the remarks of the speakers today, that vaccination, if carried out strictly in accordance with modern ideas of what proper vaccination is, will produce some modification of the severity of the attack. It seems also pretty well proved that vaccination does no harm. If it does harm, it is generally in the direction of causing abscesses, and this is clearly an error in technique. But if the technique

is carefully adhered to, I think all workers are agreed that vaccination does no harm. Therefore, we are amply justified in continuing our efforts along these lines.

Now we shall proceed to do our best with the questions submitted.

DR. DOULL.—The question is asked: According to available evidence, how long is immunity thought to last in those successfully inoculated?

I do not think I shall attempt to answer that question because I do not think there is any evidence that whooping cough vaccine prevents the disease at all.

DR. MUCKENFUSS.—The question is asked: Since mortality from pertussis decreases rapidly after the second year, would you immunize children over that age?

I should have to follow through Dr. Doull's line of reasoning. With a disease as unpleasant as whooping cough, even without any significant mortality, I think it would be well worth while to immunize at almost any age to prevent going through the agony. On the other hand, I do not see any evidence that immunization prevents the disease.

Another question is: One investigator has advocated twice the suggested Sauer vaccine. Is this of value?

I am wholly unable to answer that question, but if twice the dose recommended by Sauer gives twice as severe a reaction on inoculation, I should say it is almost as bad as the disease.

A third question: Is the complement fixation reaction helpful in the diagnosis of whooping cough? Is it an index of immunity?

The complement fixation test in 90 per cent of the cases will become positive after the third or fourth week of the disease. At that late date you may get the laboratory to confirm your diagnosis. There will be a certain number of individuals who may have had an exposure and who will give a positive fixation at times in the absence of the disease, but that is relatively rare except in older individuals.

As to variation in determination of immunity, until we get some convincing evidence of the actual rôle of these antibodies in the protection from disease, I do not think it is possible to make any statement as to that.

DR. DOULL.—The question is asked: Can you state an age level below which immunization should not be attempted and why?

Dr. Madsen gave whooping cough vaccine to a number of newborn babies and two died. Perhaps the safest rule is not to treat those under six months. I would leave that to the judgment of the pediatrician.

Another question relates to possible modification of attack: I think we are all at a loss to say whether or not whooping cough vaccine modifies an attack. I would be inclined at the present time to give it in the hope that we might modify the attack. How much should a pediatrician promise? I should say that he should promise nothing, and he will not be disappointed.

Both of the following questions assume that immunity to attack follows use of the vaccine, with which I do not agree.

The first is: Is there any evidence that the method of administration affects the immunity obtained?

I do not know of any evidence. Practically all workers give the vaccine subcutaneously. American workers, following Dr. Sauer, usually use much larger doses than Dr. Madsen.

The second is: About what percentage of immunity is developed in the first month after inoculation?

Dr. Sauer states that immunity develops slowly. Dr. Madsen thinks it develops early. The Cleveland study shows no evidence of immunity judging from comparative attack rates, for inoculated and control subjects, either early or later.

DR. MUCKENFUSS.—The question is: It has been stated by Sauer that pertussis immunization should not be followed or preceded within a period of four months by other immunization. If that is true, why?

I have no information on that point. I do not know of any reason why any such period should elapse between different types of immunization.

Question: Can we justify expenditure in public health departments to continue experiments?

I should say we could justify public expenditure for experimentation on any disease which is the cause of illness and mortality. Experiments along the same particular line are being done in one place or another. It may be a matter for judgment, but I certainly think that money can and should be spent for investigation in connection with any disease that is of any consequence.

Question: Does not the literature indicate that better results are obtained with twenty billion organisms per cubic centimeter?

I do not think the literature indicates that. Opinions differ quite widely.

Question: Is there enough protein in 8 c.c. of Sauer vaccine to produce an anaphylactic reaction?

It is unlikely that any bacterial vaccine will produce an anaphylactic reaction unless injected intravenously.

Question: Can one advocate the Sauer vaccine as a routine measure on the basis of facts presented this afternoon?

That is a personal opinion. I do not think so.

Question: Does one attack of pertussis confer permanent immunity?

I think practicing pediatricians have occasionally seen mothers have a second attack with the child.

Question: Does not vaccination give a mother a sense of false security and make it more likely she will not isolate the child soon enough?

I rather imagine that depends on what she was told when the vaccination was given. If she was led to expect anything, I should think that would be true. That is rather difficult to answer.

Question: After all this excellent discussion, what is the majority of the members in the audience to do about pertussis immunization in common everyday practice?

I rather think the chairman should answer that.

DR. DOULL.—The question asked is: I have seen tonsillitis, acute pharyngitis, in one instance, follow within forty-eight hours after an injection of Sauer vaccine. That is in contrast to the reaction often seen after diphtheria toxoid. Do you believe that general resistance to disease is lowered by whooping cough inoculation?

Upper respiratory symptoms have not come to our attention. I cannot answer the second part of the question.

In Cleveland the nurses visited the homes of a considerable number of children in the evening after injection and again the next morning. The injections were given usually between 10:00 and 11:00 A.M. In the afternoon a rise of temperature was sometimes observed. Some local reaction usually occurred, persisting for about seventy-two hours. In the late afternoon following the first dose, of 97 children observed, 11 had rectal temperatures of 38.1° C. or over and 3, temperatures of 39.0° C. or over; of 101 observed following the second dose, 18 had temperatures

of 38.1° C. or above, and 5, of 39.0° C. or over; and of 91 observed following the third dose, 11 had temperatures of 38.1° C. or over and 3, of 39.0° C. or over. Fever on the morning following inoculation was infrequent. Three children are stated to have had convulsions within twelve hours following inoculation. In one the convulsions were observed by our nurse.

Question: How long is the average case of whooping cough contagious?

I suppose the average case is contagious for about three weeks. In about 50 per cent of the cases positive cultures can be obtained during the third week. In some, the bacillus can be recovered as late as the sixth or seventh week.

DR. STALLINGS.—The question is: Do the members of the profession keep the vaccine in the refrigerator or is it carried around in the bag? Are members giving appreciably larger doses to older children?

The vaccine should be kept in the refrigerator. Since most of the injections are given in the office, it would seem unnecessary to carry it around in the bag. No mention was made in the questionnaire of giving larger doses to older children.

Question: What is the longest period you can wait between inoculations if an intercurrent contagious disease arises?

I cannot answer this question positively because we do not know enough about the length of time required to build up immunity. However, if the contagious disease causes the child to be much below par, it would not be wise to give the injections until the child is back to normal. Whether the whole series should be given again, we will know only by further study.

Question: Sauer's vaccine is a suspension of a macroscopic precipitate. Is it not possible that the caliber of a 26 gauge needle will prevent the passage of such a precipitate and hinder results?

From a practical standpoint, the number 24 gauge needle is safer to use for children. The rather concentrated suspension will pass through a 24 gauge needle without difficulty.

Question: Is any vaccine or antigenic substance of value in the treatment of pertussis?

Yes (Krueger), pertussis U.B.A., which has been on the market since June, 1933, is of definite value in the treatment of pertussis. Good results are obtained in about 70 per cent of cases treated, if the injections are given daily for about ten days, in the average case. Daily injections are necessary because the relief from symptoms comes within two to three hours after the injection and lasts about twenty to twenty-four hours. The probable mechanism is a rapid desensitization.

When the antigen was first put on the market for clinical trial, there was a short period during which the antigen was inactivated in shipping. That was most unfortunate, for some physicians who used it at that time were greatly disappointed in their results. We have recently analyzed our data on a series of cases treated during the past year and find we are still getting 70 per cent good results. These figures have been confirmed by a number of practicing pediatricians. Recently, questionnaires were sent to 162 pediatricians who had used the (Krueger) pertussis U.B.A. in the treatment of over 3,700 cases of pertussis. Sixty-three per cent reported that they had obtained good results.

Question: Is blood sedimentation of value in the early diagnosis of pertussis?

I am familiar with but one study published. It is doubtful whether the procedure is of value in early diagnosis.

Question.—How do you explain coughing and choking and occasional vomiting that may occur with the immunizing doses? Is there any advantage in the double injection method of immunization usually advocated for those children?

It is possible that these children have had subclinical infections and that a massive dose of antigen produced a local shock reaction in the sensitized bronchi. If these symptoms developed to a marked degree, my inclination would be to decrease the amount of vaccine given at each injection for the remainder of the series. In order to give the same total amount as ordinarily used, one or two more injections might be required.

The object in giving two injections at one time is to avoid severe local reactions, such as sterile abscesses from giving too large an amount at one site.

DR. MUCKENFUSS.—The question is: Will not the repeated injections of the various serums, vaccines, toxins, and toxoids in the individual child create a sensitivity that may finally result fatally in the sensitive child? May they not antagonize one another?

Immunologically, antigens are fairly specific so that one antibody has no influence against another. There are some that are related, but the general principle will still hold true; there is no reason why the injection of one antigen causes reaction against another under ordinary circumstances.

CHAIRMAN McINTOSH.—The question is asked: Would it be advisable for the Academy or for the American Public Health Association to set up a model procedure so that the results of various studies may be had for analysis?

I would suggest that this be referred to the Committee on Scientific Research.

As the time for this panel has expired, it will be necessary now to close.

REPORT OF THE MEETING OF REGION II OF THE AMERICAN ACADEMY OF PEDIATRICS

Region II of the American Academy of Pediatrics met in New Orleans on Dec. 1 and 2, 1937, in conjunction with the Section on Pediatrics of the Southern Medical Association. The Academy meetings were held in the forenoons and the Section meetings in the afternoons. Eighty-one members of the Academy registered. Each received a copy of the yearly report of the Region.

On the first morning there were four round tables, as follows:

1. "Mental Health in Children," conducted by Dr. Horton Casparis, professor of pediatrics, Vanderbilt University, Nashville, Tenn.

2. "Whooping Cough Immunization," by Dr. Louis W. Sauer, Evanston, Ill.

3. "Poliomyelitis," by Dr. Archibald Hoyne, associate clinical professor of pediatrics, University of Chicago, and Dr. Gilbert J. Levy, associate professor of pediatrics, University of Tennessee School of Medicine, Memphis, Tenn.

4. "Allergy in Childhood," by Dr. George Piness, Los Angeles, Calif.

The round table discussions on allergy and mental health in children were held at Tulane University. The discussions on whooping cough immunization and poliomyelitis were held at Louisiana State University.

The section on allergy was well attended. A large number of members of the Southern Medical Association who were not pediatricians but were interested in this branch of medicine, were present and took an active part in the discussion. The other round table discussions were so isolated from the auditorium, where the main convention of the Southern Medical Association was held, that they were attended only by a small number of pediatricians. They did not, therefore, in any way fulfill the purpose for which they were intended because all four were arranged principally for the general practitioner. The discussions were repeated on the following morning, the attendance being less on the second day than on the first. For this reason, it was thought by those in charge of the meeting that this scheme of alternating with the Pediatric Section of the Southern Medical Association on the same days is not a success: that probably it will be better for the Academy to hold the regional meetings at some separate time and place.

The business meeting, held in the auditorium of Tulane University, was well attended. As an introduction, the chairman stated that there were three principal subjects for discussion: the national meeting, the regional meeting, and the state meeting.

The question of the national meeting was first considered. Dr. J. C. Overall, of Nashville, Tenn., offered a motion that Region II go on record as being in favor of holding the national Academy meeting at a separate time, at a separate place, and entirely independent from the American Medical Association, and that its delegates be so instructed. The motion was duly seconded, and after much discussion, was carried.

The next discussion concerned the time of the regional meeting. It was decided that a committee, consisting of Dr. Harvey Garrison, Dr. L. W. Holloway, and Dr. H. Leslie Moore, be appointed to meet with Mr. Loranz to make arrangements for holding the regional meeting with that of the Southern Medical Association in Oklahoma City next year. It was further decided that the type of the meeting to be held in Oklahoma City be left to the judgment of the state chairman of Oklahoma and members from that state.

The meeting closed with a discussion as to who should be eligible for admission to the Academy. The members voted that Region II should go on record as advocating that only those who limit their work to pediatrics be considered eligible.

The state chairman of Oklahoma reports that on Oklahoma Day, which will be Tuesday before the meeting of the Section, seven pediatric papers will be read: one, of an hour's length, to be given by the honor guest, who has not yet been chosen, the remainder to be fifteen-minute clinical talks by well-known pediatricians. On Wednesday afternoon there will be two round table discussions, followed by the business meeting, and later the banquet, which will be held in conjunction with the Section on Pediatrics of the Southern Medical Association.

The headquarters for the pediatricians will be at the Skirvin Hotel. The committee requests that all pediatricians who intend to be present at this joint session of Region II and the Southern Medical Association write at once for reservations, as hotel accommodations will be limited and those who apply first will receive preference.

Oklahoma City is centrally located. The committee is preparing an excellent program, and it is hoped that the entire region membership of 244 will attend.

Reports of State Chairmen

Alabama.—No report.

Arkansas.—No report.

Florida.—Organized activity is handled largely through the medium of the Florida Pediatric Society. An enthusiastic meeting was held during April at St. Petersburg in connection with the annual meeting of the state medical association. Round table discussion groups were led by Academy members. Attendance of the general practitioner and laymen at the sessions manifested widespread interest in the program. A project for the Academy during the coming year is an attempted survey of the Florida Crippled Children's Home at Gainesville. Dr. Earl Carlson has expressed an interest in the classification and segregation of those cases which may respond to a program of muscle reeducation and group study. Some service is rendered to the agencies administering Title 5 of the Society Security Act. At the suggestion of the Committee on Child Health Relations, representatives have been appointed in various sections of the state to serve actively and in an advisory capacity with existing agencies concerning maternal and child health. These representatives also expect to function with the committee chosen from the state medical association for maternal and child welfare. Medical consultation has been provided for the orthopedic division of the Florida Crippled Children's Bureau.

The short course of graduate instruction for doctors of medicine in Florida was held at Orlando for five days during June. Dr. A. J. Schaffer, of Baltimore, was lecturer for pediatrics. The postgraduate course was well attended and provided an opportunity for the doctors in the rural sections and smaller towns to become informed concerning current programs in medical science.

Under the auspices of the Florida State Tuberculosis Association and sponsorship of the Rosenwald Foundation a series of lectures was given for the negro physicians in Miami, July 6-31, 1937. Childhood tuberculosis was discussed by Academy members.

Regional meetings foster a closer feeling of fellowship. The Academy member obtains a clearer view of the general policies and aims of the Academy and thus increases his individual interest. It is the feeling of Academy members in Florida that membership should not be offered to those who do not limit their work to pediatrics. We would like to see the standards raised, not lowered, and feel very definitely that it is an honor and privilege for membership to be conferred upon a pediatrician. The honor carries with it a responsibility toward the child and the practitioner. The work of the Academy will be carried forward better in the hands of those whose interests are devoted wholly to pediatrics.

Through the medium of committee work and by an improved spirit of cooperation with existing agencies, better opportunity for academy service will be provided. The spirit of the membership is excellent. We are expecting in Florida a year of steady progress in finding new ways to serve—rather than a year of outstanding achievement.

WARREN W. QUILLIAN
State Chairman

Georgia.—The American Academy of Pediatrics has continued to carry on the work of previous years in close cooperation with the Georgia Pediatric Society.

Members of the Academy acting as a liaison committee of the Child Health Relations Committee have served in an advisory capacity to the three agencies administering Title 5 of the Social Security Act in Georgia.

The Child Health and Welfare Council held no annual meeting in 1937. During the summer a plan has been worked out with the state Departments of Health and Welfare whereby demonstrations will be attempted in twelve counties in the state. Community participation in matters of child health and child welfare will, of course, be the feature of the work. A meeting of the professional persons concerned in this work in each county will be held in Atlanta on September 27. The groups asked to attend this meeting include the county health officer, the county health nurse, the county welfare worker, the child welfare worker, and certain district supervisors in both the health and welfare fields. The purpose of this meeting will be to give these workers a clear conception of the plan and enlist their aid in obtaining more active lay participation in their community.

Later in the fall, after these local county councils have been reorganized by health and welfare workers, it is our plan to hold a meeting in each county. Speakers from the Georgia Pediatric Society and from the state Departments of Health and Welfare will present the problems confronting the community and propose definite projects to be fostered by the county councils. The projects in the health field will stress (1) prenatal clinics, (2) health clinics for infants and children, and (3) immunization clinics.

M. HINES ROBERTS
State Chairman

Kentucky.—As state chairman of the American Academy of Pediatrics for Kentucky, I beg to report that we have had a successful year in many respects. I feel that the most important thing that we are doing at present is the education of the physicians and laity in the value of pediatric advances.

1. Our postgraduate course of instruction at the Children's Free Hospital has closed another successful session.

2. We have had the past summer an intensive course of ward rounds and lectures given to the colored physicians in the colored ward of the city hospital.

3. We have conducted an all-day pediatric meeting consisting of papers, a large clinic, and round table conferences in connection with our state medical society meeting. At this meeting we had papers presented by men, largely nonmembers of the Academy who are interested in pediatrics, the Academy members bringing out a very lively discussion. The meeting was attended by physicians from all over the state who were encouraged to take part in the discussion. Papers presented will be printed in our state medical journal. The clinic and round table conferences were conducted by members of the Academy who have had experience in teaching. I believe that this increases the interest of the general practitioner and the meetings which we have held have been quite well received by the profession and encouraged by the state medical society. In addition to this, we had papers presented on pediatric problems on the regular program of the state society.

4. We have continued our policy of sending out pediatric teams to important centers of the state to hold clinics and conferences and to make talks before luncheon clubs and Parent-Teachers' Associations on pediatric problems. We have also aided in the round-up of the preschool children in the schools of Louisville.

5. The meetings of the staff of our Children's Free Hospital have been thrown open to physicians at large and some of them attend these meetings which are practically clinical presentations of the most interesting cases in the hospital.

The State Department of Health has appointed a new head for the Department of Maternal and Child Welfare. As chairman of the advisory board of this department, we have had several conferences and it is hoped that we will be able to work out together short courses on obstetrics and the care of the newborn to be held at strategic points.

In the reorganization of the state government the wife of a pediatrician has been made head of the Welfare Department. Contacts have been made, and it is hoped that some plan may be formulated for utilizing pediatricians in this important part of social work. One must be appalled at the diversity and complexity of the problems which affect the care of the oncoming generation.

PHILIP F. BARBOUR
State Chairman

Louisiana.—No report.

Mississippi.—Dr. John K. Bullock, of Jackson, Miss., has been named as co-chairman for Mississippi.

The Academy continues as heretofore, to exert its influence individually through the state pediatric society and other medical organizations.

Lectures constituting a postgraduate course in pediatrics are being given at different points in the state by Dr. Robert A. Strong, of the Department of Medicine, Tulane University. The different medical associations of the state and Tulane University are sponsoring this work.

While no official vote has been taken by the Academy members, the almost universal opinion is that the members of the Academy should be only those who limit their work to that specialty. We are agreed that if a member of the Academy moves into another region and does not limit his work to pediatrics, the members of that state have the right to say whether he shall continue as a member. I hope our region will go on record at the meeting as favoring the proposition that when a man begins general practice, he automatically loses membership in the Academy.

N. C. WOMACK
State Chairman

North Carolina.—The activities in the Maternal and Child Health Services which have been carried on in North Carolina during the quarter ending June 30, 1937, are being conducted under the auspices of the state Board of Health, under the direction of Dr. George Cooper, secretary of the board, who from time to time has been assisted by an advisory committee, upon which your chairman represents the American Academy of Pediatrics.

ALDERT S. ROOT
State Chairman

Oklahoma.—The Oklahoma Pediatric Society met in Tulsa last May. In connection with the regular scientific program a symposium on pediatric economics as it applies to Oklahoma was given. The Society is cooperating with the Oklahoma Society for Crippled Children in its work with the infantile paralysis cases. The total number of cases reported in the state for the first eight months of 1937 is

double that of any previous year. This does not necessarily mean that Oklahoma has twice as many cases. Allowance must be made for a much improved reporting system.

The Oklahoma Commission for Crippled Children, through its field nurses, is attempting to contact every reported case, in cooperation with the local physician. Parents are instructed as to the follow-up care. They are urged to go to an orthopedic surgeon, if they are financially able; if not, most of them will be cared for through the out-patient department of the Crippled Children's Hospital.

The directors of the Oklahoma Public Welfare Commission have authorized the continuance of the cooperative agreement whereby state assistance money is used to supplement the crippled children's fund of the various counties. The state money will act as an equalization fund and will go to the counties of greatest need. Before a county can qualify for aid it must make a showing to the effect that it has complied with the provisions of the Oklahoma law for crippled children in every detail and show that its crippled children's fund is exhausted for the current fiscal year.

Parents of indigent children needing hospitalization will go before the county court. If the judge finds the case a worthy one, he will sign the commitment papers and send them and the family to the county welfare worker for investigation and endorsements. Papers are forwarded to the state welfare office and then to the Oklahoma Commission for Crippled Children. True emergency cases can be short-circuited into the hospital and the necessary forms and investigation will follow.

CLARK H. HALL
State Chairman

South Carolina.—South Carolina under the Social Security Act has established well baby clinics throughout the state. We hold from two to three of these clinics in each county a month. The clinics are diagnostic clinics except where the medical society in the county does not object to the giving of toxoid.

Prenatal clinics were held in each county throughout the state. There were 1,135 prenatal examinations; 816 of these were colored patients; 974 Wassermanns were done; 22 per cent were positive.

A significant figure in the children's clinics in South Carolina was the 680 deaths from prematurity; 76 per cent of these deaths were probably due to syphilis.

To summarize the well baby clinics, 25 per cent showed malnourishment or underweight, 25 per cent showed signs of rickets.

D. LESESNE SMITH
State Chairman

Tennessee.—In addition to continuing postgraduate work given to general practitioners in the medical schools, which work is largely contributed to by members of the Academy, and in addition to the various attempts Academy members are making to stimulate general practitioners to take better care of children through the appearance of Academy members on local medical society programs; still every effort is being made by the child welfare committee of the state medical society (composed of members of the Academy) in cooperation with the director of maternal and child health in the State Health Department (an Academy member) to formulate a more extensive teaching program throughout the state. This postgraduate program in pediatrics has been delayed, some waiting for a similar course in obstetrics to end.

Further, members of the Academy are cooperating closely with lay organizations, especially Parent-Teachers' groups in the promotion of child health in an attempt to place more emphasis on the health care of children from birth and to entrance into school. Academy members are also contributing to the promotion of a more effective educational program in the field of tuberculosis by demonstrating through the care of children what their specific problem is and how children may be used

in a correlation of the broader aspects of the tuberculosis problem. There was also cooperation with the National Association for Nursery Education and one of the Academy members, upon request, assumed the chairmanship of the health division of that organization at its biennial meeting.

It will be seen from the above that no formal program has been instituted; however, it has been felt that it is more effective for the Academy members to cooperate with other organizations in the promotion of better child care.

HORTON R. CASPARIS
State Chairman

Texas.—No new activities were inaugurated, but the members and the state chairman have cooperated with the various health organizations in their activities throughout the year. The program of the refresher courses, sponsored by the state health department and the state medical association and carried out throughout the state by a pediatrist and an obstetrician, have all been conducted by Academy members.

The medical section of the Conference of Child Health and Protection, held in Austin in February, was ably presided over by Dr. Thomas McCrummen, of Austin, and the state chairman participated in the discussions.

A meeting was held of all the Academy members in the state during the meeting of the state medical association in Fort Worth. Dr. E. C. Mitchell, regional chairman, and Dr. H. Leslie Moore, of the regional board, and nineteen members of the Academy attended.

The advisory board of the Crippled Children's Division of the State Health Department recently appointed to its staff Dr. Edwin G. Schwarz, Fort Worth, Dr. W. B. Carrell, Dallas, and Mr. Rober Jolly, Superintendent of Memorial Hospital in Houston.

EDWIN G. SCHWARZ
State Chairman

Virginia.—The Department of Clinical and Medical Education of the Medical Society of Virginia in cooperation with the University of Virginia, the Medical College of Virginia, the Virginia State Department of Health, and the Children's Bureau of the United States Department of Labor has continued to conduct postgraduate (refresher) courses in obstetrics and pediatrics throughout the state. During the past year two full-time clinicians have been engaged in this work. Dr. L. L. Shamburger began work as clinician in obstetrics and gynecology on July 1, 1936, succeeding Dr. Maxwell Lapham, who had conducted courses in these subjects during the two preceding years. Dr. Jay M. Arena began work as clinician in pediatrics on Oct. 1, 1936, with courses in this subject similar to those given in several sections of the state by Dr. George M. Lyon and Dr. Sam Ravenel during the two preceding years. These courses have been given with the approval and cooperation of the local county medical societies and have been well received, especially in the isolated sections of the state and in the smaller communities. Dr. Arena resigned his position the first of September and was succeeded by Dr. Robert B. Hightower, who will continue this work in pediatrics. Dr. Shamburger is continuing the courses in obstetrics and gynecology.

The Bureau of Maternal and Child Health, administering the Maternal and Child Health Services of the Social Security Act, has organized 49 prenatal, postnatal, and well-baby clinics, conducted by local physicians in those cities and counties having a health officer to attend to the administrative side of these clinics. An important part of this work has been the prevention of neonatal syphilis.

During the past year a Bureau of Venereal Diseases has been established by the State Health Department with Dr. L. J. Roper as Director. This Bureau, to-

gether with the Bureau of Maternal and Child Health, is directing particular attention toward the control of syphilis in pregnant women, as the best means of combating the problem of congenital syphilis. The importance of serologic examination is stressed, and midwives are instructed to direct their patients to clinics or physicians where these tests can be made.

The services for crippled children are administered by a Bureau of the State Health Department with Dr. E. C. Harper as Director. A state-wide survey is being made and a central file established where a record is made of all crippled children in the state. Funds have been made available for the care of all indigent crippled children.

The child welfare services are being administered by the State Department of Public Welfare.

Both the State Commissioner of Health (Dr. I. C. Riggin) and the Commissioner of Public Welfare (Mr. Arthur James) have welcomed the proffer of the Academy membership to serve in an advisory capacity.

The University of Virginia and the Medical College of Virginia have continued to hold their yearly postgraduate clinics with pediatrics included in the program. In June the annual two-week St. Phillip Hospital Postgraduate Clinic for practicing colored physicians was conducted by the staff of the Medical College of Virginia. Members of the Academy have taken part in all of the above postgraduate clinics.

The Virginia Pediatric Society, which includes the Academy members, is continuing its policy of holding each spring a yearly clinical meeting, to which the profession at large is invited.

The chairman and five other members of the Child Welfare Committee of the Medical Society of Virginia during the past year, were members of the Academy. This Committee has made a careful review of the activities in the state pertaining to child care and stated in its recent report to the Medical Society of Virginia: (1) that agencies and machinery have been set up to cope with almost all phases of child welfare; (2) that funds for the functioning of such agencies, except in the case of crippled children, are in most instances very inadequate; (3) that the problems of child health and welfare in the state are now largely a matter of providing financial support necessary for the proper functioning of existing agencies.

The committee has specifically called attention to the need of the State Board of Education for more adequate facilities to care for the mentally subnormal children; and the desirability of expanding the work of the Department of Public Welfare to include all dependent children in the state. It reports that, although a great deal has been done for indigent children with defective vision, the funds appropriated to the Commissioner for the Blind are very inadequate. It finds that there is pressing need for more state-supported beds for children in the state sanatoriums for tuberculosis, although certain changes contemplated in the near future will improve this condition to some extent.

There has been a gratifying reduction in the incidence and mortality from diphtheria, but the committee thinks that provision of free toxoid for indigent children would lead to further reduction.

The Committee reports that excellent work is being done in the prenatal, postnatal and well-baby clinics and believes these will prove an important factor in the reduction of infant mortality. The Bureau conducting this work is, among other things, handicapped by lack of funds for employing sufficient nursing personnel. As soon as funds are available it is thought desirable to have the work of these clinics expanded to take in the "runabout child." At present there appears to be a gap in the supervision of the child between the age of two years and the preschool age.

There is a state appropriation for the care of the teeth of indigent children. This work is under the supervision of a Bureau of the State Health Department, but,

as in the case of the other agencies mentioned, appropriations are not sufficient to provide dental facilities for all indigent children of the state.

As a result of its study of the Child Welfare Committee, in its report to the Medical Society of Virginia, has urged this body to exert its influence toward securing more liberal appropriations by the legislature for the particular needs found to exist.

Although the Academy as a unit has not undertaken any activity of its own, it is felt that through the work of its members on active committees, and through their advisory service to other organizations it is serving a useful purpose.

J. B. STONE
State Chairman

West Virginia.—The Academy Fellows in West Virginia have been active individually during the past year, although as a unit we have never set a definite objective. The Child Health Advisory Committee of the West Virginia Medical Association, under the chairmanship of Andrew E. Amick, has rendered valuable service in an advisory capacity to the state health department in its direction of the maternal and child hygiene program for the state.

All the Fellows actively supported the bill for compulsory vaccination against smallpox and immunization against diphtheria of all children entering the public schools of West Virginia for the first time. This bill was passed by the legislature, signed by the governor and became a law with the opening of schools this fall. West Virginia as far as we can ascertain, is the first state to pass a law requiring both immunizations. The response of parents with preschool children has been gratifying. It would be a safe wager that more vaccinations against smallpox have been done this year than in any previous ten-year period.

The Academy membership has also taken active part in popularizing early immunizations. We feel that this is a valuable service and already results are being shown by earlier immunizations both in private practice and in the clinics.

The state was fairly well covered by preschool conferences during the late spring and summer. No effort is being made to restrict these conferences to children deserving this service. We feel that this can and should be done, and we shall work toward its accomplishment.

The postgraduate courses were well received in most places this summer. Obstetrics, pediatrics, and syphilis were the subjects covered. It was felt that a small matriculation fee for these lectures and round tables might lead to a better response and more regular attendance at the conferences. With this end in view, a charge of $5 was made, but the results were disappointing. Toward the end of the courses, the fee was dispensed with. Men of outstanding reputations were used as leaders this year, and the increase in attendance as the courses went along testified as to the wisdom of this policy. There are still a few practitioners that are suspicious of these courses, even though they are given under the sponsorship of the state health department and the West Virginia Medical Association. They fear some connection with state medicine. The type of leaders, all being men in clinical practice, and the type of instruction have helped to remove this fear and I believe each year will see an increase in attendance.

Academy members have also been active in their respective counties in assisting in working out health programs for the public schools under the new county unit system of education. Different plans are being developed, according to the needs of the community. It will probably be impossible to work out a single type of program that will solve the problems in each county, but we believe, from the plans being evolved, certain guiding principles will be standardized leading to the ultimate end of better health supervision and instruction for all public school children.

J. LEWIS BLANTON
State Chairman

Academy News

Eighth Annual Meeting of the American Academy of Pediatrics

The program for the eighth annual meeting of the American Academy of Pediatrics, which will be held at the Hotel Del Monte, Del Monte, Calif., June 9, 10, and 11, 1938, has been announced. Registration will begin at 9:00 A.M. Thursday, June 9. The round table discussions of which there will be twelve, each given twice, will begin at 2 o'clock each of the three afternoons.

Thursday, 2 P.M. Round Table Discussions

TITLE	LEADER
Administration of Fluids.	Francis Scott Smyth, M.D. San Francisco, Calif.
Body Mechanics.	Clifford Sweet, M.D. Oakland, Calif.
Clinical Immunology.	K. F. Meyer, M.D. San Francisco, Calif.
Convalescent Serum Therapy.	C. M. Hyland, M.D. Los Angeles, Calif.
Dental Caries.	Harold Noyes, D.D.S., M.D. Chicago, Ill.
School Health.	Harold H. Mitchell, M.D. Astoria, N. Y.
Sulfanilamide.	Paul Hamilton, M.D. Alhambra, Calif.
Whooping Cough.	Harold K. Faber, M.D. San Francisco, Calif.

At 5 P.M. the meeting of the State Chairmen is scheduled with dinner following.

Thursday, 8 P.M. Scientific Papers

Spasmophilia of the Newborn.	Harry Bakwin, M.D. New York, N. Y.
Pathology of Light.	Lloyd E. Hardgrave, M.D. San Francisco, Calif.

Friday, June 10, 8:30 A.M.

Cinema on the Phenomena of Allergy.	Bret Ratner, M.D. New York, N. Y.

Friday, 9:00 A.M. Panel Discussions

Allergy.	Bret Ratner, M.D. New York, N. Y.
Thymus.	A. Graeme Mitchell, M.D. Cincinnati, Ohio.

Friday, 2:00 P.M. Round Table Discussions

Clinical Immunology.	K. F. Meyer, M.D. San Francisco, Calif.
Convalescent Serum Therapy.	C. M. Hyland, M.D. Los Angeles, Calif.

TITLE	LEADER
Dental Caries.	Harold Noyes, D.D.S., M.D. Chicago, Ill.
Diabetes.	H. C. Shepardson, M.D. San Francisco, Calif.
Nursing Technique.	Jay I. Durand, M.D. Seattle, Wash.
Psychology.	Mary Helen Layman, M.D. San Francisco, Calif.
Rheumatic Fever.	T. Duckett Jones, M.D. Boston, Mass.
School Health.	Harold H. Mitchell, M.D. Astoria, N. Y.

The banquet will be held at 7 o'clock Friday.

On Saturday morning, June 11, the general meeting will begin at 9:30 A.M. At this time the president's address will be heard and the following reports, copies of which will be presented in mimeographed form to the membership, will be considered: Report of the Executive Board, report of the Secretary-Treasurer, reports of regional committees, and reports of special committees.

After new business is disposed of, the general meeting will close with the installation of the new president.

Saturday, 2 P.M. Round Table Discussions

Administration of Fluids.	Francis Scott Smyth, M.D. San Francisco, Calif.
Body Mechanics.	Clifford Sweet, M.D. Oakland, Calif.
Diabetes.	H. C. Shepardson, M.D. San Francisco, Calif.
Nursing Technique.	Jay I. Durand, M.D. Seattle, Wash.
Psychology.	Mary Helen Layman, M.D. San Francisco, Calif.
Rheumatic Fever.	T. Duckett Jones, M.D. Boston, Mass.
Sulfanilamide.	Paul Hamilton, M.D. Alhambra, Calif.
Whooping Cough.	Harold K. Faber, M.D. San Francisco, Calif.

Hotel Accommodations

All hotel accommodations are on the American plan, that is, room with meals. The Hotel Del Monte offers a variety of accommodations in the east wing, main building, west wing, or cottages. *Write immediately for reservations.*

One can get to Del Monte either from San Francisco or from Los Angeles. It is about 125 miles south of San Francisco and some 300 miles north of Los Angeles.

When you buy your ticket, buy to Chicago and get rates from Chicago on. The railroads east of Chicago do not give any rates, but rates can be obtained from Chicago west and south. Remember in buying your ticket to buy a round trip ticket, and also remember that you have the choice of several routes going out and coming back. It is so arranged that west of Chicago, one can go out by one route and come back by another. For instance, one can go directly to San Francisco and be routed back by way of Los Angeles or Seattle without any extra charge. There is an extra charge for routing through Canada. This charge, however, is nominal.

If you wish to enjoy the trip, be careful about your itinerary. There are many places of interest between the East and California which should be included.

Dr. Louis C. Schroeder

Dr. Louis C. Schroeder, of New York City, died on Feb. 25, 1938. He had been incapacitated for some time by a weakened heart so that his death was not unexpected. He has been an active physician and his extensive interests have carried him into many medical affairs. His death is keenly felt by many friends, and he will be a loss to all the various associations he had formed.

He graduated in medicine from Columbia University, College of Physicians and Surgeons, in 1911. He was Assistant Professor of Clinical Pediatrics in Cornell University, New York, and Physician-in-Chief to the New York Nursery and Child's Hospital for several years. He was a Fellow of the American Medical Association, a member of the New York Academy of Medicine, of the Harvey Society, the American Pediatric Society, to which he was elected in 1925, and a Fellow of the American Academy of Pediatrics. He was elected to the executive board and served as chairman of Region I of the Academy. As chairman of Region I, he contributed a great deal to the outstanding success of the two annual meetings of the Academy in New York City in 1935 and in 1937. As an organizer of Academy interests and activities in the eastern states, he did a splendid job, bringing together various individuals and groups and leading to a better understanding and conception of the purpose of the Academy in this important region.

He played a prominent part in the White House Conference in 1931, in the now extinct American Child Health Association, and in many other child welfare organizations of this country.

His charming personality endeared him to patients and to many friends both in and out of the profession. The JOURNAL records with great regret his unfortunate and untimely death.

The meeting of Region III will be held at the Statler Hotel, Detroit, Mich., October 27, 28, and 29, 1938. There will be a morning meeting at the University Hospital, Ann Arbor, Mich., with a football game Saturday afternoon for those who care to go.

The annual postgraduate course in pediatrics will be conducted under the auspices of the American Academy of Pediatrics, the University of Michigan, Wayne University, and Michigan State Medical Society at the Henry Ford Hospital, Children's Hospital of Michigan, Herman Kiefer Hospital on April 18, 19, 20, 1938. The committee for the Academy is composed of Dr. Thomas B. Cooley, Dr. David Levy, Dr. Edgar E. Martmer, and Dr. J. A. Johnston, chairman.

A symposium on the physical appraisal of the normal school child will be held by representatives of various specialties—ophthalmology, otology, cardiology, orthopedics. Under the Detroit plan, school examinations are conducted by the family physician. The need for a more general understanding of what constitutes an adequate "screening" process for the commoner defects is generally admitted, and if this plan is to function satisfactorily, a plan of detecting at least the gross departures from the normal in vision, hearing, posture, and heart and lung defects, as well as a uniform set of recommendations on prophylaxis, is imperative.

News and Notes

The **American Board of Pediatrics** announces the following examinations:

Detroit, Mich.—Definite date not set. Examination to be held at the time of the meeting of Region III of the American Academy of Pediatrics, Oct. 27, 28, and 29, 1938.

Rochester, N. Y.—Definite date not set. Examination to be held at the time of the meeting of Region I of the American Academy of Pediatrics, Nov. 11 and 12, 1938.

Oklahoma City, Okla.—Nov. 15, 1938, preceding the joint meeting of Region II of the American Academy of Pediatrics and the Southern Medical Association.

Information has been received from the **Pediatric Abstracts Club** of London, extending an invitation to any American pediatrists who may be visiting England during the coming summer to attend its meetings which are held at the Hospital for Sick Children (Great Ormond Street, London, W.C. I), on the third Wednesday of each month at 8:15 P.M. The group is composed of young pediatrists, and its meetings are informal.

The next meeting of the **Society for Pediatric Research** will be held at the Berkshire Inn in Great Barrington, Mass., on the afternoon of May 4 and the morning of May 5.

The **American Pediatric Society** will also meet at Great Barrington, Mass., on May 5, 6, and 7, 1938. The first day's meeting will include a joint program with the **Society for Pediatric Research.** Dr. Kenneth D. Blackfan is President of the American Pediatric Society. This is the Semicentennial Anniversary of the founding of the American Pediatric Society.

The **Chicago Tumor Institute** will open March 21, 1938. It will offer consultation service to physicians in the diagnosis and treatment of cancer and radiation facilities for cancer patients. The institute also proposes to conduct research and to offer training to physicans who may wish to qualify as specialists in the study and treatment of this disease.

The **Emma Pendleton Bradley Home,** East Providence, R. I., an endowed hospital for children with neurologic and behavior disorders, offers training in neuropsychiatry of childhood.

Six-month residencies with remuneration for physicians qualified by previous pediatric training are available. Also six-month interneships for graduates of acceptable medical schools are available.

How New York state is providing for the rehabilitation of its mental defectives who are capable of material improvement and for the humane custodial care for persons of such a low grade of development that they cannot be restored to community life is discussed in a newly published report of the survey of the

methods of care, treatment, and training of the feebleminded at Letchworth Village, one of the state's largest institutions for the mentally deficient. Upon request to the office of the president, 74 Trinity Place, New York City, a copy of the report may be obtained by qualified physicians.

Sir Frederick Truby King, of Wellington, New Zealand, died on Feb. 9, 1938. He was one of the important figures in the history of child welfare throughout the world. He was an Honorary Member of the American Pediatric Society. He observed early in his career that when young calves were fed on a "rational scientific artificial feeding" the mortality was greatly reduced. Like many other pioneer physicians, he applied observations in nature to children with startling and satisfactory results. He founded in Dunedin the principle of cottage management of infants ill with diarrhea with outstanding success. His fame spread throughout New Zealand and to England and America, and his work was fully recognized as a Truby King System for the care and treatment of babies and for the training of nurses.

Leading British and American physicians, 6,000 miles apart, will confer via the radio on the greatest menace to child health, rheumatic heart disease. This conference, the first international broadcast on any health problem is arranged by the radio committee of the **American Heart Association**, New York City, and will observe National Child Health Day.

Lord Thomas Jeeves Horder, Physician-in-Ordinary to the King of England, will open the conference speaking from London. Lord Horder's aerial report will dwell upon public health aspects of the disease, particularly in England. Dr. William J. Kerr, president of the American Heart Association, will take up the discussion from San Francisco. Dr. Kerr will tell of the work of the association in this field. The radio audience will then be switched back to Atlantic City to hear Dr. Homer F. Swift, of the Rockefeller Institute, New York City, describe the medical investigations being carried on to isolate the cause of the disease. Dr. T. Duckett Jones, of the House of the Good Samaritan, Boston, will follow with a discussion of the treatment of children with crippled hearts, emphasizing the need for long-continued sanatorium care.

This international conference-broadcast was conceived by a committee of Irvington House, sanatorium for the care of children with heart disease at Irvington-on-Hudson, N. Y., in an effort to stimulate greater public interest and action in this major child health problem. It will acquaint doctors, and particularly parents and teachers, with the challenge of rheumatic heart disease. The present difficulty in arousing the attention of the public to rheumatic heart disease lies partly in its undramatic nature. It is not easy, without specific education, to recognize the first slow manifestations of rheumatic heart disease as the onset of a systemic disease which may forever cripple the heart of a child.

Book Review

Erythroblastic Anemia. J. CAMINOPETROS. Monographs of the Academy of Athens, Vol. VI, No. 3, 141 pages and 59 illustrations.

This monograph, printed both in Greek and in French, is of peculiar interest as being the first extensive discussion of this disease to emanate from its presumptive land of origin, though the author has published several brief articles on different phases of the subject during the past three years.

Caminopetros states that between 1927, when the first case was recognized, and 1934, 42 cases of erythroblastic anemia were observed, scattered through all parts of Greece except Macedonia and Thrace. Since 1935 his own studies have covered 34 cases, of which he presents the details of blood and roentgenographic studies in tabular form. He subdivides his cases into three groups: (1) erythroblastic anemia with complete mongoloid facies; (2) "anemie des geophages," a type in which the anemia has been slower in development, the facies are not so marked, and all of the patients have been observed to be dirt-eaters. Why the author should have selected this symptom to distinguish the group is not clear, as he states his belief that it has no etiological significance, and he says, moreover, that it has been observed since the time of Hippocrates to be a symptom common to many forms of chronic anemia. (3) His third group is that of erythroblastic anemia in infants.

In contrast to these groups he cites some cases of anemias of other types observed during the same period—curable anemias, syphilitic anemia, hemolytic icterus, etc. He discusses also the question of the anemia of von Jaksch-Hayem-Luzet, which he considers to be a secondary form. He reports a single case of sickle-cell anemia in a child of Bulgar-Thessalian origin, his discussion of which leaves it a little uncertain whether he does not think of this as a special form of erythroblastic anemia.

Caminopetros' studies have led him to the conclusion that the most important diagnostic criterion of erythroblastic anemia is an increase of the resistance of the red cells to hypotonic saline (this is common both in erythroblastic anemia and in sickle-cell anemia). In all of the cases which he recognizes as genuine, hemolysis began at 3.8 or below and was complete at 2.4 or less. He discusses the other characteristics of the blood, but does not find them so convincing.

The author has noted the familial character of the disease, so often commented on, finding in eleven of thirty-two families at least two children affected, and in one an aunt and niece. He has found the disease in more than one generation in four families, in one of which three successive generations were affected. He has also found the increased resistance which he considers characteristic to be common in apparently healthy relatives of patients. These observations lead him to the conclusion that the disease is hereditary and may extend so as to threaten the whole Greek people. In support of this idea he cites reports that the remains of the Mayan Indians show evidences of a disease which like erythroblastic anemia, to which their ultimate disappearance has been ascribed.

The bone changes have occupied much of Caminopetros' attention, especially those in the skull, which produce the mongoloid appearance. He has enlisted the assistance of a professor of anthropology in the study of this question. They are agreed that the "mongoloid eye," of which they make much, is not inherited in this disease, but is common to a large proportion of the cases, a result of the bone

marrow changes. It seems that in parts of Greece there is a considerable admixture of mongoloid blood, and one of their patients with erythroblastic anemia showed Mongolian spots and proved to have had a Mongol ancestor. There is a discussion of differences in the bone changes of erythroblastic anemia and those of other diseases affecting the marrow.

One interesting suggestion is made regarding a possible method of treatment. In a patient who developed malaria while under observation Caminopetros noticed an amelioration of the blood picture sufficient to encourage him to make a trial of inoculation of other patients with the plasmodium. This procedure is now under way, and a case is cited in which the nucleated cells disappeared after the inoculation. No conclusions are drawn as yet.

The 59 photographic illustrations include 6 microphotographs of blood films; 24 photographs of patients with their parents, among which is one of the two adults observed with the disease; 5 of children in families of Mongol ancestry; 18 radiographs of bones of patients and their parents; and 6 radiographs of bones in other blood disorders.

The monograph is a real contribution to our knowledge of this interesting disease, especially with regard to its probable hereditary character.

T. B. C.